AD_____

Award Number: DAMD17-00-2-0018

TITLE: Mechanisms in Chronic Multisymptom Illnesses

PRINCIPAL INVESTIGATOR: Daniel J. Clauw, M.D.

CONTRACTING ORGANIZATION: University of Michigan
Ann Arbor, MI 48106-0737

REPORT DATE: October 2007

TYPE OF REPORT: Annual, Option II

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01-10-2007	Annual, Option II	1 Jul 2006 – 30 Sep 2007

4. TITLE AND SUBTITLE

Mechanisms in Chronic Multisymptom Illnesses

5a. CONTRACT NUMBER

5b. GRANT NUMBER
DAMD17-00-2-0018

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Daniel J. Clauw, M.D.

Email: dclauw@med.umich.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Michigan
Ann Arbor, MI 48106-0737

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
The overall objectives of this cooperative agreement are to conduct research in pursuit of identifying the physiologic mechanisms responsible for the symptoms of pain, fatigue, and memory difficulties commonly seen in patients with Chronic Multisymptom Illnesses (CMI) (i.e., fibromyalgia, chronic fatigue syndrome, Gulf War Illnesses, etc.); to identify the risk factors for developing these syndromes as well as programs aimed at both preventing these illnesses and treating established cases. These objectives will be achieved through multiple research studies using innovative, technologically advanced (e.g., functional MRI and telemedicine) methodologies in a multidisciplinary environment. Various studies will be conducted to explore all aspects of pain processing, the effects of exercise deprivation and sleep reduction on symptomatology, the ability of exercise and/or cognitive behavioral therapies to alter patients' locus of control for pain, the neurobiological mechanism(s) of acupuncture on analgesia, the presence of hypersensitivity to auditory stimuli, and the effectiveness of cognitive behavioral therapy delivered via telemedicine and the internet. These studies will be conducted on well-characterized cohorts of CMI subjects and healthy controls taken from our burgeoning subject registry. Research continues at the University of Michigan, Ann Arbor, MI and Avera Research Institute, Sioux Falls, SD.

15. SUBJECT TERMS
chronic multisymptom illnesses, fibromyalgia, Gulf War Illness, chronic pain

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
U	U	U	UU	212	USAMRMC

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

Table of Contents

Mechanisms in Chronic Multisymptom Illnesses
PI: Daniel J. Clauw, MD
Annual Report 2006-2007
DAMD 17-00-2-0018

INTRODUCTION:

Researchers in the Chronic Pain and Fatigue Research Center (CPFRC) and collaborators within the University of Michigan and at Avera Research Institute in Sioux Falls, SD are conducting research on human subjects in pursuit of the following overall objectives: to identify the physiologic mechanisms responsible for three prominent symptoms (pain, fatigue, and memory difficulties) of Chronic Multisymptom Illnesses (CMI) (i.e., fibromyalgia [FM], chronic fatigue syndrome [CFS], Gulf War Illnesses, etc.); and to identify the risk factors for developing these syndromes, as well as programs aimed at both prevention of these illnesses and treatment of established cases. These objectives will be achieved in a multidisciplinary environment with use of innovative, technologically advanced methodologies (e.g., using functional MRI [fMRI] and Positron Emission Tomography [PET], assessments of sensory processing, autonomic, and hypothalamic pituitary adrenal functions) and use of the internet and telemedicine to disseminate an educational intervention.

BODY:

The Specific Aims of this overarching research program are to continue to develop a registry of research subjects and healthy controls to be applied to ongoing recruitment efforts; to extensively study the cognitive, psychological and neurobiological measures of pain processing in this spectrum of illnesses; to determine whether an established non-pharmacological intervention (Cognitive Behavioral Therapy [CBT]) is effective when administered using an internet-based educational intervention; to explore both the physiologic and treatment effects of exercise and sleep on these illnesses; to study the neurobiological and psychological risks for developing these illnesses after an episode of trauma (in this case motor vehicle accident); to determine if individuals with FM suffer from an overall heightened sensitivity to physical stimuli (in this case auditory); to examine the effects of relaxation therapy and exercise training on pain locus of control, specifically to determine whether these interventions can alter patients' pain locus of control from an external to an internal drive; to study the neurobiological mechanism(s) of acupuncture analgesia from a Western perspective on patients with FM. These Aims are being addressed in eight individual research studies, each of which is described below with a brief overview of the study and a status update as of the writing of this report.

All interested participants who visit the CPFRC complete an extensive screening protocol, the Subject Registry, before participating in a specific study. Once screened, participants will then take part in the study or studies for which they qualify. A series of studies (titles in bold) will be performed at the University of Michigan and at Avera Research Institute as indicated below.

University of Michigan, Ann Arbor, MI:

1. **Subject Registry for Interdisciplinary Studies of Chronic Multisymptom Illnesses at the University of Michigan**

Study Overview: This protocol involves the development of a centralized subject registry that (a) recruits interested volunteers, (b) provides a general first-level screening of participants, and (c) informs volunteers of current or future studies for which they might undergo a non-redundant and briefer study-specific screening. In addition to the demographic information gathered during initial phone contacts, the screening process generates a spectrum of information on each candidate regarding their general physical and psychiatric (Axis I and II) status, their specific CMI symptomatology, and the influence/interplay of CMI symptoms on their life. The subject registry also serves as a repository for genetic studies that will examine the genetic polymorphisms that are associated with a higher risk of developing these disorders.

Status/Results to date: Over the past 12 months, we have recruited 125 new subjects. This brings our total number of subjects for the Registry to 504. We have continued to schedule and screen individuals for enrollment in the CPFRC Subject Registry.

Although the inclusion/exclusion criteria for the Registry has remained stable, recruitment efforts have become more 'targeted'. Over the last year, we have recruited prospective research candidates for purposes of participating in specific, ongoing hypothesis-based studies. This has minimized the disappointment and frustration previously voiced by candidates who successfully completed the screening process but were then unable to participate in specific studies.

Given that the majority of our studies include brain imaging, candidates are thus cautioned that being left-handed or claustrophobic, using opioid medications on a maintenance basis, and/or having a BMI above 36 may exclude them from participation in studies involving brain scans.

As mentioned above, the Registry is currently a repository for genetic information. In the near future, a new, hypothesis-driven protocol will be submitted to the DOD HSRRB to seek approval to complete genetic analyses using data from subjects who consented to have their DNA collected and stored.

2. The Effect of Exercise and Sleep Deprivation on the Development of CMI Symptoms

Study Overview: The broad aim of the current project was to evaluate the individual and synergistic effects of two different lifestyle disruptions: exercise and sleep deprivation. Our underlying hypothesis is that some individuals are prone to symptom development while others are not. It is this group of susceptible runners in whom we are interested. We think that a subset of them will present with physiological markers of an attenuated physiological stress response that acts as a diathesis for the potential development of chronic multi-symptom illnesses, like FM and Gulf War Illness.

Eligible individuals included those who were between the ages of 18-40 years, who regularly ran 5 or more days per week and who also routinely slept between 7-9 hours per night. Participants were followed for 7-days of baseline, 10-days of a restriction period, and 7-days of follow-up. Prior to restriction we evaluated autonomic nervous function, the hypothalamic pituitary adrenal axis, and symptom report. During the restriction phase participants kept daily records of pain and fatigue symptoms and completed a more detailed series of symptom questionnaires approximately 2/3 of the way through the 10-day period. During the follow-up phase, we repeated the baseline testing battery and had participants complete a final series of symptom questionnaires on their final day in the study.

Status/Results to date: We enrolled 112 (56F, 56M) individuals into the current protocol. Of these individuals, 95 completed participation and 17 withdrew prior to completing the study. The most common reasons for withdrawal were time constraints and unrelated illness/injury. Only 1 participant withdrew because of his group assignment (exercise deprivation). Our primary recruitment strategies were word-of-mouth and the University of Michigan's centralized clinical research site (Engage). We have since ended recruitment and enrollment for this study and are now embarking on the analysis phase of the project.

We first looked at the effect of our deprivation schemes on symptom development using a 2 (pre/post deprivation) x 2 (sleep restriction) x 2 (exercise deprivation) ANOVA. There was a significant main effect for sleep restriction for all symptom domains (pain, fatigue, mood and cognition). For example, clinical pain [$F(1,80)=8.79$, $p=.04$] and fatigue [$F(1,80)=37.00$,$p<.001$] increased while mood [$F(1,80)=13.41$, $p<.001$] and perceived dyscognition worsened [$F(1,80)=10.98$, $p=.001$]. Exercise deprivation resulted in modest increases in pain, fatigue and mood, but not in dyscognition. There were no significant interactions between the two stressors.

We next explored the association between baseline (prior to deprivation) autonomic nervous system activity and symptom report. Several heart rate variability parameters were correlated with increased pain and cognition symptoms ($r=-.57$, $p<.001$) and ($r=-.357$, $p<.05$, respectively). None of these parameters were significantly associated with negative mood or increased fatigue.

Thus, at first look, it appears that among healthy regularly exercising and sleeping individuals, disruption of their normal routine was associated with increased somatic symptoms. From this sample we can further suggest that a segment of healthy symptom-free individuals possess certain baseline neurophysiological characteristics that predict subsequent symptom development.

The above analyses represent our initial foray into the data. We are currently awaiting our final data to be processed and will continue to explore our diathesis hypothesis using logistic regression to evaluate the ability of different measures to predict group membership (symptomatic vs. asymptomatic).

Two abstracts reflecting preliminary results will be presented at the upcoming annual scientific conference of the American College of Rheumatology. These abstracts are appended to this report.

3. Outcome of Patients Seen in the Emergency Department (ED) after Motor Vehicle Collision (MVC)

Study Overview: This study examines the neurobiological and psychological predictors of chronic symptoms such as regional or widespread pain, depression, or post-traumatic stress disorder (PTSD) following a stressful traumatic event: a motor vehicle accident. Just as with the above study, our pilot data suggest that the autonomic and HPA measures taken within the ED are predictive of the development of chronic pain or PTSD following such trauma. Individuals that are seen in the ED immediately following a motor vehicle accident that do not have a head injury, fracture or require hospitalization receive an extensive testing paradigm, including psychophysical testing and psychological assessments in the ED. These individuals are followed for 6 months and tested again with the same paradigm. Individuals in this study also undergo fMRI testing to examine predictor of chronic pain after a traumatic event. In addition to identifying physiological and psychological characteristics that predict the development of

chronic pain or PTSD following this type of trauma, we have applied for DOD, NIH and CDC funding to perform a companion treatment trial examining whether a beta blocker (propanolol) will prevent the development of these chronic symptoms in a sub-group of high-risk individuals seen in the ED after MVC.

Status/Results to date: Recruitment for this study began in early 2006 and is currently ongoing. All participants who remain in the study will be assessed 3-7 days after MVC, again at 1 month following MVC, and finally, at 6 months following MVC. As of this report, 140 subjects have completed the study through the 1-month follow up time point. All subjects who are currently enrolled are expected to complete their participation within the next 6 months. Complete data analyses will continue following subject study completion.

Preliminary findings indicate that demographic (age, income), symptom (pain, depression, anxiety), and cognitive (thoughts about pain and fault) characteristics affect the resolution of neck pain symptoms in patients.

Additional findings from pilot data indicate that a relatively small number of baseline predictors provide excellent prediction of persistent musculoskeletal pain after MVC at both 1-month and 6-month follow up. These predictors include demographic (age, race), psychological (dissociative symptoms at the time of the MVC, initial patient estimate of the time until physical recovery), physiological (general health, autonomic function), and initial symptom factors (pain, anxiety). Further exploration into racial disparity indicates that African Americans may experience a higher incidence of moderate or severe neck or back pain after MVC than European Americans. However, we recognize that further work is needed to understand this difference more completely.

Three abstracts reflecting these preliminary results will be presented at the upcoming annual scientific conference of the American College of Rheumatology. These abstracts are appended to this report.

4. Mechanisms of Acupuncture Analgesia

Study Overview: In an innovative mix of modern technology and alternative therapies, we are using acupuncture as a potential placebo, and fMRI, PET, and magnetic resonance spectroscopy (SPECT) to determine specific neurological mechanisms of placebo analgesia. Within this study, we will better define opioidergic mechanisms that underlie pain and the placebo effect. Our preliminary data from this study suggest that patients with fibromyalgia have evidence of increased occupation of mu opioid receptors at baseline, suggesting that their endogenous opioidergic systems are maximally activated and in spite of this they are still experiencing severe pain. If these findings are confirmed it may help explain why opioid drugs are not clinically effective in chronic pain conditions such as fibromyalgia. Additional findings are listed below.

Status/Results to date: As of this report, 35 subjects have completed their participation in this study and 1 subject is currently in process. Recruitment is ongoing to employ SPECT technology.

Three abstracts containing preliminary results have been accepted for presentation during the upcoming annual conference for the American College of Rheumatology. In addition, three abstracts were presented at the annual scientific conference of the American Pain Society. The complete abstracts with detailed results are included in the appendices. Major findings from each of the abstracts include: 1) Using PET technology in a longitudinal study pre- and post-acupuncture or sham treatment (9 treatments over 4 weeks), significant changes in μ-opioid

receptor binding potential were detected between treatment acupuncture and sham acupuncture within 17 different brain regions suggesting that the underlying mechanisms of regular acupuncture treatment and sham acupuncture treatment are not equivalent, despite similar results in clinical pain report. 2) Using proton magnetic resonance spectroscopy (H-MRS) to investigate variations in glutamate (Glu) and glutamine (Gln) levels over time in FM patients, we have observed that these levels appear to change with improvements in multiple pain dimensions within FM patients. 3) In addition, these data are the first to associate Glu and Gln levels with working memory function in FM.

Data from this study will continue to be analyzed per study protocol. The results will be published and will contribute to the larger body of work being developed by the study PI (Richard E. Harris, PhD) in his subsequent project entitled "Developing Biomarkers for Fibromyalgia" that will be completed under a separate protocol recently funded by the USAMRMC.

5. Pain Mechanisms in Chronic Multisymptom Illnesses (CMI)

Study Overview: This study aims to assess sensory processing abnormalities in CMI. Methods include various psychophysical paradigms (ascending stimuli, random stimuli, pressure, temperature, etc.) and fMRI to extensively examine the activity of endogenous analgesic systems including descending antinociceptive activity (diffuse noxious inhibitory controls [DNIC]), aberrant afferent sensory stimuli processing, and abnormal cortical and sub-cortical central nervous system function in groups with various CMI. This study also examines the extent to which cognitive or psychological processes affect pain processing in both normal individuals and individuals with these illnesses. Finally, this study will explore whether individuals with chronic pain may have a global disturbance in sensory processing by concurrently measuring auditory threshold and pain thresholds.

Status/Results to date: As of this report, 95 subjects have been enrolled in this study. This study is actively recruiting subjects to continue to examine descending antinociceptive (diffuse noxious inhibitory controls [DNIC]) activity, as well as overall sensory abnormalities, in individuals with chronic pain states and in normal healthy individuals. Data analysis and presentation of results via scientific conference proceedings, publications or future research pursuits is anticipated in the remainder of 2007, into 2008.

6. Locus of Pain Control: Neural Substrates and Modifiability

Study Overview: Our preliminary study showed that individuals with an internal locus of pain control (i.e., they felt they could do something about their pain) had different neural processing of pain (based on fMRI), and less overall pain, than individuals with an external locus of pain control (who felt that they could not control their pain). In this study, we will evaluate the effectiveness of two non-pharmacological methods of improving pain locus of control in patients with FM: (a) training in relaxation and (b) training in aerobic fitness (exercise). A standard care group of FM patients and a group of healthy controls will round out the 4 study arms. We will use real-time symptom monitoring and extensive psychological assessment to characterize subjects, and again use fMRI to measure pain processing. We hypothesize that modifying an individual's cognitions or thoughts about their pain in this manner will lead to neurobiological differences in pain processing on fMRI from the patient's baseline assessment to their assessment after they have had the relaxation or exercise interventions.

Status/Results to date: Recruitment for this study began in August 2005 and is currently ongoing. To date, 92 subjects have been recruited for this study. Subjects have been recruited into all 4 arms of the study in a random permuted blocks strategy that randomly assigns the first 5 FM subjects to one of the three arms, the next five FM subjects to one of the remaining two arms and the last 5 FM subjects to the remaining arm. Healthy controls are recruited into the final comparison arm. This randomization strategy permits the interventions to be conducted in a group format. Thus far, we are on schedule to complete 25 subjects in each arm, and recruitment is anticipated to end in Fall 2007.

Preliminary data from the current study using fMRI both before and after a behavioral intervention for FM compared neuronal activation patterns at baseline and post-treatment in a group with worsening clinical pain and a group that improved. Results suggest that increases or decreases in clinical pain in FM are associated with corresponding changes in neuronal activation patterns in brain regions involved in pain processing. In what may be the first look at longitudinal fMRI data, this study suggests that even over fairly long periods of time, fMRI of pain processing is relatively stable in FM patients in whom there is no significant change in clinical symptoms.

These preliminary results will be presented at the upcoming annual conference of the American College of Rheumatology in November 2007 (2 abstracts are appended to this report). More complete results from the main study hypothesis and objectives will be examined with subsequent publications anticipated in 2008.

Partnership with Avera-McKennan Research Hospital, Sioux Falls, SD:

7. Internet and Telehealth Enhanced CBT for the Management of Fibromyalgia

Study Overview: This non-pharmacologic treatment intervention is designed to test the efficacy and efficiency of delivering CBT to persons with CMI using telemedicine and internet approaches. Further, this study will develop and test the efficacy of a multidisciplinary educational CD given to chronic pain patients to improve pain and fatigue symptoms as well as function and overall quality of life. This project is being pursued with the Avera-McKennan Research Hospital. Given that as many as 14% of active duty personnel experience chronic symptom-based conditions and that this spectrum of illness occurred much more frequently after the Gulf War and other deployments, this project could have enormous impact on how these service members receive healthcare.

Status/Results to date: The website and CD development were recently completed and integrated with the electronic data capture system so that this entire study is online. Subject recruitment began in August 2006 and is currently ongoing. As of this report, 108 subjects have been enrolled.

The content of the multidisciplinary educational CD covers three main topic areas: overview of fibromyalgia including a discussion of causes and treatment advice; symptom management including medications and cognitive behavioral therapy skills such as exercise, sleep, relaxation, and pleasant activities; and lifestyle management such as goal setting, problem solving, pacing, reframing, and communication. The educational CD contains standardized video lectures, homework assignments to practice skills learned, and an interactive goal tracking feature. This CD is also available as a website, which contains a chat room accessible to study participants and a link to electronic self-report forms. Web access is restricted to study participants who have signed a consent form, obtained a study id, and created a password. Since

this site is not accessible to the general public, several screen shots have been included in the appendices to give examples of content and appearance.

Preliminary results indicate that patients in the intervention have experienced notable improvements in clinical pain severity and physical function compared to the standard care group. These patients have made good use of most of the intervention strategies, with emphasis on exercise training, relaxation techniques, pleasant activity scheduling, and goal setting skills. Patients in the intervention arm have actively used the CD and the internet and have reported receiving a high quality of healthcare from the intervention that has helped them to deal effectively with their FM symptoms.

These preliminary analyses are encouraging and have prompted the CPFRC and the Avera study teams to meet in September 2007 to discuss the current status of the study, to determine a study end date and plans for complete data analysis, and to explore future research ideas that may derive from the success of this trial. Upon completion of all subjects, data analysis will commence and continue into 2008 at which time abstracts and manuscripts will be developed.

Other Notable Findings and Activities:

Impaired cognitive function, euphemistically labeled "fibro-fog," is a common complaint in patients with FM. In an analysis of working memory, we examined whether cognitive impairment could be the result of a faster rate of decay in FM patients compared to healthy individuals. Our results indicate that difficulty managing competing or distracting information is the root of working memory problems in FM, rather than a more rapid loss of information from working memory. These results will be presented at the upcoming annual scientific conference of the American College of Rheumatology (abstract appended).

Over the years, results from our collective studies have continually suggested that CMI are more similar than they are different. In other words, accumulating evidence indicates that these illnesses may be stemming from overall sensory dysfunction such that patients who have long been known to share common symptoms of pain sensitivity, fatigue, and cognitive difficulties, may also share sensitivity to sound, may experience vertigo, in general, may have greater sensitivity to a host of sensory experiences. We continue to examine these avenues via pilot studies with junior faculty mentees and collaborations with other researchers within in and outside of the University of Michigan.

In May 2007, the CPFRC hosted a research consortium at the University of Michigan, entitled "Chronic Somatic Symptoms Consortium." UM and invited practitioners and researchers from diverse backgrounds in industry, academia and federal organizations shared their ideas on chronic pain treatment, recognition, diagnosis, research and future directions. By addressing the important role in which chronic pain treatment impacts the community – patients, clinicians, researchers, and industry – the interactions and exchanges of knowledge and ideas discussed in this consortium were aimed at leading to improved communications and collaborations regarding research, treatment and recognition for patients with chronic pain.

Finally, over the past year members of our research team have participated in campus and community-wide outreach efforts including speaking to the UM medical research community regarding clinical research coordinating and adverse event reporting; communicating latest research findings and research opportunities to support group leaders; providing education and opportunities for research participation to interested patrons of community-based health fairs and patient advocacy groups; presenting abstracts at the UM Internal Medicine Research Day; and

maintaining educational websites that focus on Gulf War Illness and chronic multisymptom illnesses including a list of the Center's publications and other reputable websites, and a description of who we are and what research opportunities exist within the Center.

KEY RESEARCH ACCOMPLISHMENTS:

- In the exercise/sleep deprivation study (study #2 above), we have observed that certain healthy individuals who experience a disruption of their normal exercise and/or sleep routines will develop autonomic nervous system activity and somatic symptoms similar to those that characterize CMI patients. Likewise, the MVC study (study #3 above) is beginning to show evidence of physiological and psychological predictors of persistent pain symptoms in certain patients who did not experience pain prior to the MVC. Both of these studies are demonstrating that **baseline** abnormalities in autonomic and hypothalamic pituitary adrenal function predict the subsequent development of somatic symptoms. This could represent a major paradigm shift in how these illnesses are viewed because, previously, we thought these abnormalities were causing the illness. This would also make it possible for the DOD to screen recruits for autonomic and HPA function and identify those who might be at risk of various sequelae following exposure to stress.
- In the past few years, the field of pain genetics has grown substantially. With burgeoning evidence for hereditary links in fibromyalgia, this field has gained interest in our research group. Given the data for autonomic dysfunction in patients with FM, Gulf War Illness and CFS, we examined the rate of polymorphisms involving candidate genes involved in catecholamine synthesis. Our preliminary data suggest a fairly strong association between possessing a certain minor allele and the presence of CMI such as FM, CFS, and GWI. These data need to be replicated in a larger sample; however, these results provide tangible evidence for the long suspected genetic links in these illnesses. These results will be presented at the upcoming annual scientific conference of the American College of Rheumatology (abstract appended).
- In aggregate our functional imaging studies continue to show a number of objective abnormalities in pain processing in individuals with chronic multisymptom illnesses. Perhaps the most remarkable finding is that it appears as though the endogenous opioid system is already maximally activated in patients with fibromyalgia because at baseline the mu opioid receptor binding is diminished, and this value correlates strongly with clinical pain ratings. This important data is providing evidence for biomarkers and technology that may be beneficial in diagnosing, predicting, and ultimately, treating these illnesses.
- The treatment study underway looking at electronic media to help manage fibromyalgia represents the "cutting edge" of the pain field and could be useful in a number of clinical settings if shown to be effective. Preliminary results to date are positive, indicating that patients who have used this technology to experience a therapeutic intervention have engaged in the activities provided and have reported good outcomes.

REPORTABLE OUTCOMES:

The following list of journal articles, published book chapters, manuscripts submitted for review and abstracts presented during the period of this report or accepted for presentation during upcoming scientific conferences fully describes the reportable outcomes that have resulted from this research:

Journal Articles – 2006, not previously reported (pdfs of each are appended unless otherwise noted by *)

Bingham CO, Buckland-Wright JC, Garnero P, Cohen SB, Dougados M, Adami S, Clauw DJ, Spector TD, Pelletier JP, Raynauld JP, Strand V, Simon LS, Meyer JM, Cline GA, Beary JF. Risedronate decreases biochemical markers of cartilage degradation but does not decrease symptoms or slow radiographic progression in patients with medial compartment osteoarthritis of the knee: results of the two-year multinational knee osteoarthritis structural arthritis study. Arthritis Rheum. 2006 Nov;54(11):3494-507.

Clauw DJ, Harris RE. Is acupuncture more effective than sham acupuncture in relieving pain in patients with low back pain? Nat Clin Pract Rheumatol. 2006 Jul;2(7):362-3.

Geisser ME, Roth RS, Williams DA. The allure of a cure. J Pain. 2006 Nov;7(11):797-9; discussion 804-6.

Harris RE, Clauw DJ. How do we know that the pain in fibromyalgia is "real"? Curr Pain Headache Rep. 2006 Dec;10(6):403-7.

Hsu MC, Clauw DJ. A different type of procedure for a different type of pain. Arthritis Rheum. 2006 Dec;54(12):3725-7.

Hunscher D, Boyd A, Green LA, Clauw DJ. Representing natural-language case report form terminology using Health Level 7 Common Document Architecture, LOINC, and SNOMED-CT: lessons learned. AMIA Annu Symp Proc. 2006;:961.

Mori DL, Sogg S, Guarino P, Skinner J, Williams D, Barkhuizen A, Engel C, Clauw D, Donta S, Peduzzi P. Predictors of exercise compliance in individuals with Gulf War veterans illnesses: Department of Veterans Affairs Cooperative Study 470. Mil Med. 2006 Sep;171(9):917-23.

Myklebust M, Colson J, Kaufman J, Winsauer J, Zhang YQ, Harris RE. Policy for therapeutic acupuncture in an academic health center: a model for standard policy development. J Altern Complement Med. 2006 Dec;12(10):1035-9.

Williams DA, Gracely RH. Biology and therapy of fibromyalgia. Functional magnetic resonance imaging findings in fibromyalgia. Arthritis Res Ther. 2006;8(6):224.

Journal Articles – 2007 (pdfs of each are appended unless otherwise noted by *)

Banzett RB, Gracely RH, Lansing RW. When it's hard to breathe, maybe pain doesn't matter. Focus on "Dyspnea as a noxious sensation: inspiratory threshold loading may trigger diffuse noxious inhibitory controls in humans". J Neurophysiol. 2007 Feb;97(2):959-60.

Boyd AD, Hosner C, Hunscher DA, Athey BD, Clauw DJ, Green LA. An 'Honest Broker' mechanism to maintain privacy for patient care and academic medical research. Int J Med Inform. 2007 May-Jun;76(5-6):407-11.

*Clauw DJ. Fibromyalgia: update on mechanisms and management. J Clin Rheumatol. 2007 Apr;13(2):102-9.

Csako G, Costello R, Shamim EA, O'hanlon TP, Tran A, Clauw DJ, Williams HJ, Miller FW. Serum proteins and paraproteins in women with silicone implants and connective tissue disease: a case-control study. Arthritis Res Ther. 2007 Sep 17;9(5):R95 [Epub ahead of print]

*Eliav E, Kamran B, Gracely RH, Benoliel R. Evidence for Chorda Tympani Dysfunction in Burning Mouth Syndrome patients. J Orofacial Pain. 2007 May;138(5):628-33.

Geisser ME, Gracely RH, Giesecke T, Petzke FW, Williams DA, Clauw DJ. The association between experimental and clinical pain measures among persons with fibromyalgia and chronic fatigue syndrome. Eur J Pain. 2007 Feb;11(2):202-7.

Gracely RH, Undem BJ, Banzett RB. Cough, pain and dyspnoea: Similarities and differences. Pulm Pharmacol Ther. 2007;20:433-437. Epub 2007 Jan 10

*Gracely RH. pain psychologist's view of tenderness in fibromyalgia. J Rheumatol. 2007 May;34(5):912-3

Harris RE, Clauw DJ, Scott DJ, McLean SA, Gracely RH, and Zubieta J-K. Decreased Central μ-Opioid Receptor (MOR) Availability in Fibromyalgia (FM). J Neuroscience. 2007 Sept;27(37):10000-10006.

Mease P, Arnold LM, Bennett R, Boonen A, Buskila D, Carville S, Chappell A, Choy E, Clauw D, Dadabhoy D, Gendreau M, Goldenberg D, Littlejohn G, Martin S, Perera P, Russell IJ, Simon L, Spaeth M, Williams D, Crofford L. Fibromyalgia syndrome. J Rheumatol 2007;34(6):1415-25.

*Petrou M, Harris RE, Foerster BR, Mclean SA, Sen A, Clauw DJ, and Sundgren PC. Proton MR Spectroscopy in the Evaluation of Fibromyalgia Patients: Comparison with Healthy Controls and Correlation with Symptom Severity. Am J Neuroradiology. 2007, *in press*.

*Reed BD. Sen A, Gracely RH. Effect of test order on sensitivity in vulvodynia. J Reproductive Medicine 2007;52:199-206.

Sundgren PC, Petrou M, Harris RE, Fan X, Foerster B, Mehrotra N, Sen A, Clauw DJ, Welsh RC. Diffusion-weighted and diffusion tensor imaging in fibromyalgia patients: a prospective study of whole brain diffusivity, apparent diffusion coefficient, and fraction anisotropy in different regions of the brain and correlation with symptom severity. Acad Radiol. 2007 Jul;14(7):839-46

Williams DA, Park KM, Ambrose KR, Clauw DJ. Assessor status influences pain recall. J Pain. 2007 Apr;8(4):343-8. Epub 2007 Jan 16.

Manuscripts Submitted for Review in 2007 (pdfs of each are appended unless otherwise noted by *)

Harris RE, Sundgren PC, Pang Y, Hsu M, Petrou M, Kim SH, McLean SA, Gracely RH, Clauw DJ. Dynamic Levels of Glutamate within the Insula are Associated with Improvements in Multiple Pain Domains in Fibromyalgia (FM). Arthritis Rheum, 2007, *accepted with revisions.*

*Petrou M, Harris RE, Foerster BR, Mclean SA, Sen A, Clauw DJ, and Sundgren PC. Proton MR Spectroscopy in the Evaluation of Fibromyalgia Patients: Comparison with Healthy Controls and Correlation with Symptom Severity. Am J Neuroradiology. 2007, *accepted with revisions*.

Abstract Presentations –

(Note: All 2006 abstracts were presented in last year's annual report.)

2007 (pdfs of each are appended)

Clauw DJ, Belfer I, Max M, Williams DA, Gracely RH, McLean SA, Harris RE, Neely A, Bair E, Diatchenko L, Maixner W. Increased Frequency of the Minor Allele for beta-3 Adrenergic Receptors in Individuals with Fibromyalgia and Related Syndromes. Accepted by the American College of Rheumatology 71st Annual Scientific Meeting, Boston, MA, Nov 7-11, 2007.

Glass JM, Harris RC, Sundgren PC, Pang Y, Gracely RH, Clauw DJ. Variation in Glutamate and Glutamine Levels within the Inslula are associated with Improvements in Working Memory in Fibromyalgia (FM). Accepted by the American College of Rheumatology 71st Annual Scientific Meeting, Boston, MA, Nov 7-11, 2007.

Glass JM, Lyden AK, Byrne-Dugan CJ, Groner KH, Ambrose KR, Grace PJ, Williams DA, Gracely RH, Clauw DJ. Effects of Sleep Restriction and Exercise Deprivation on Mood, Pain, Fatigue, Somatic Symptoms and Cognition in Healthy Adults. Accepted by the American College of Rheumatology 71st Annual Scientific Meeting, Boston, MA, Nov 7-11, 2007.

Glass JM, Lyden AK, Byrne-Dugan CJ, Groner KH, Ambrose KR, Gracely RH, Williams DA, Clauw DJ. Baseline Heart Rate Variability Predicts Changes in Pain and Cognition, but not Mood or Fatigue after Exercise and Sleep Restriction. Accepted by the American College of Rheumatology 71st Annual Scientific Meeting, Boston, MA, Nov 7-11, 2007.

Glass JM, Park DC, Crofford LJ, Fougnie D, Clauw DJ. Working Memory in Fibromyalgia Patients: Impaired Function Caused by Distracting Information, Not Rapid Decay of Stored Information. Accepted by the American College of Rheumatology 71st Annual Scientific Meeting, Boston, MA, Nov 7-11, 2007.

Harris R, Scott D, Gracely R, Clauw D, Zubieta, J. Differential changes in mu-opioid receptor (MOR) availability following acupuncture and sham acupuncture therapy in fibromyalgia (FM). J Pain (abstract supplement), 8, 4, S24, 2007.

Harris R, Scott D, Guevara M, Gracely R, Zubieta J, Clauw D. mu-Opioid receptor (MOR) binding predicts differential responsiveness to acupuncture and sham acupuncture therapy in fibromyalgia (FM). J Pain (abstract supplement), 8, 4, S49, 2007.

Harris RH, Sundgren PC, Pang Y, Khatri N, Gracely RH, Clauw DJ. Variation in Glutamate and Glutamine Levels within the Insula are Associated with Improvements in Clinical and Experimental Pain in Fibromyalgia (FM). Accepted by the American College of Rheumatology 71st Annual Scientific Meeting, Boston, MA, Nov 7-11, 2007.

Harris RE, Zubieta JK, Scott DJ, Mayo-Bond L, Gracely RH, Clauw DJ. Differential Sustained Changes in μ-Opioid Receptor (MOR) Availability Following Acupuncture and Sham

Acupuncture Therapy in Fibromyalgia (FM). Accepted by the American College of Rheumatology 71st Annual Scientific Meeting, Boston, MA, Nov 7-11, 2007.

Hsu MC, Geisser ME, Lyden AK, Williams DA, Clauw DJ. Catastrophizing and Fatigue are Associated with Poorer Perceived Physical Function Relative to Objective Activity Measures in Fibromyalgia. Accepted by the American College of Rheumatology 71st Annual Scientific Meeting, Boston, MA, Nov 7-11, 2007.

Hsu MC, Kim SH, Sundgren PC, Pang Y, Gracely RH, Clauw DJ, Harris RE. Significant Association between Changes in Glutamate Levels and fMRI BOLD Signal in the Posterior Insula of Fibromyalgia Patients. Accepted by the American College of Rheumatology 71st Annual Scientific Meeting, Boston, MA, Nov 7-11, 2007.

Mohan M, Dadabhoy D, Clauw DJ, Henry NL, Hayes DF, Stearns V, Giles JT, Storniolo AM, Ang D. Musculoskeletal Symptoms and Signs Associated with Aromatase Inhibitor Therapy in Breast Cancer. Accepted by the American College of Rheumatology 71st Annual Scientific Meeting, Boston, MA, Nov 7-11, 2007.

Patel R, Williams DA, Gracely RH, Skalski L, Chriscinske SJ, Alesi G, Clauw DJ. Functional MRI (fMRI) of Pain Processing is Stable over Time in Fibromyalgia (FM) Patients without Changes in Clinical Status. Accepted by the American College of Rheumatology 71st Annual Scientific Meeting, Boston, MA, Nov 7-11, 2007.

Robinson D, McLean SA, Swor R, Zaleski EM, Mistry Y, Schon S, Sochor MR, Newton CRH, Liberzon I, Clauw DJ. Characteristics Associated with Neck Pain Persistence versus Recovery after Minor Motor Vehicle Collision. Accepted by the American College of Rheumatology 71st Annual Scientific Meeting, Boston, MA, Nov 7-11, 2007.

Schon S, McLean SA, Mistry Y, Zaleski EM, Swor R, Robinson D, Sochor MR, Newton CRH, Liberzon I, Clauw DJ. Predictors of Persistent Moderate or Severe Neck and/or Back Pain 1 and 6 Months after Minor Motor Vehicle Collision. Accepted by the American College of Rheumatology 71st Annual Scientific Meeting, Boston, MA, Nov 7-11, 2007.

Schon S, McLean SA, Zaleski EM, Swor R, Robinson D, Mistry Y, Sochor MR, Newton CRH, Liberzon I, Clauw DJ. Racial Disparity in Pain Outcomes after Minor Motor Vehicle Collision. Accepted by the American College of Rheumatology 71st Annual Scientific Meeting, Boston, MA, Nov 7-11, 2007.

Williams DA, Patel R, Skalski L, Chriscinske SJ, Rubens M, Lapedis J, Harris RE, Gracely RH, Clauw DJ. Functional MRI (fMRI) Appears to Act as a Biomarker in Fibromyalgia (FM) by Identifying Neurobiological Correlates of Changes in Pain Over Time. Accepted by the American College of Rheumatology 71st Annual Scientific Meeting, Boston, MA, Nov 7-11, 2007.

Links to Websites:

http://www.med.umich.edu/painresearch/ - Specific to the CPFRC, updated in March 2007

http://www.med.umich.edu/gulfwarhealth/ - Specific to Gulf War Health

CONCLUSION:

Our research findings using innovative technologies like fMRI and the newer additions of positron emission tomography and magnetic resonance spectroscopy are leading to identification of biomarkers for the diagnosis, prediction, and ultimately, improved treatment of CMI.

We continue to use web technology to deliver a behavioral intervention to individuals in a rural setting who would otherwise have difficulty receiving care. Preliminary results indicate that the individuals who have been assigned to receive a cognitive behavioral intervention via web or CD have made good use of the lessons provided and are reporting improvements in symptoms and overall quality of life. This technology could substantially improve healthcare delivery in a variety of settings beyond rural.

Our research continues to observe symptom development in healthy individuals who experience either a motor vehicle collision or a disruption to their normal exercise and/or sleep routines. In both cases, a subset of individuals has developed CMI-type symptoms (pain, fatigue, mood changes) following these life events. This observation combined with their baseline autonomic and hypothalamic pituitary adrenal function provides valuable insight into the profile of an individual who appears to have a diathesis toward developing CMI. This could represent a major paradigm shift in how these illnesses are viewed because, previously, we thought these abnormalities were causing the illness. This would also make it possible for the DOD to screen recruits for autonomic and HPA function and identify those who might be at risk of various sequelae following exposure to stress.

In the past few years, the field of pain genetics has grown substantially. With burgeoning evidence for hereditary links in fibromyalgia, this field has gained interest in our research group. Given the data for autonomic dysfunction in patients with FM, Gulf War Illness and CFS, we examined the rate of polymorphisms involving candidate genes involved in catecholamine synthesis. Our preliminary data suggest a fairly strong association between possessing a certain minor allele and the presence of CMI such as FM, CFS, and GWI. These data need to be replicated in a larger sample; however, these results provide tangible evidence for the long suspected genetic links in these illnesses.

Research in CMI has grown substantially in the last few years extending our original findings in fMRI from several years ago to new frontiers in pain genetics today. Our research team has contributed substantially to the growth of understanding and treatment of these illnesses through our dedication to research and clinical care.

REFERENCES:

All references pertinent to this report are listed above in the Reportable Outcomes section with the exception of the following reference described in the Exercise and Sleep Deprivation study:

1. J. M. Glass *et al.*, *J. Psychosom. Res.* **57**, 391 (2004).

APPENDICES:

The attached appendices contain information that supplements, clarifies or supports the text, including original copies of journal articles and abstracts listed in the Reportable Outcomes section above.

APPENDICES

Journal Articles – 2006

Journal Articles – 2007

Abstracts – 2007

Journal Articles – 2006

Bingham CO, Buckland-Wright JC, Garnero P, Cohen SB, Dougados M, Adami S, Clauw DJ, Spector TD, Pelletier JP, Raynauld JP, Strand V, Simon LS, Meyer JM, Cline GA, Beary JF. Risedronate decreases biochemical markers of cartilage degradation but does not decrease symptoms or slow radiographic progression in patients with medial compartment osteoarthritis of the knee: results of the two-year multinational knee osteoarthritis structural arthritis study. Arthritis Rheum. 2006 Nov;54(11):3494-507.

Clauw DJ, Harris RE. Is acupuncture more effective than sham acupuncture in relieving pain in patients with low back pain? Nat Clin Pract Rheumatol. 2006 Jul;2(7):362-3.

Geisser ME, Roth RS, Williams DA. The allure of a cure. J Pain. 2006 Nov;7(11):797-9; discussion 804-6.

Harris RE, Clauw DJ. How do we know that the pain in fibromyalgia is "real"? Curr Pain Headache Rep. 2006 Dec;10(6):403-7.

Hsu MC, Clauw DJ. A different type of procedure for a different type of pain. Arthritis Rheum. 2006 Dec;54(12):3725-7.

Hunscher D, Boyd A, Green LA, Clauw DJ. Representing natural-language case report form terminology using Health Level 7 Common Document Architecture, LOINC, and SNOMED-CT: lessons learned. AMIA Annu Symp Proc. 2006;:961.

Mori DL, Sogg S, Guarino P, Skinner J, Williams D, Barkhuizen A, Engel C, Clauw D, Donta S, Peduzzi P. Predictors of exercise compliance in individuals with Gulf War veterans illnesses: Department of Veterans Affairs Cooperative Study 470. Mil Med. 2006 Sep;171(9):917-23.

Myklebust M, Colson J, Kaufman J, Winsauer J, Zhang YQ, Harris RE. Policy for therapeutic acupuncture in an academic health center: a model for standard policy development. J Altern Complement Med. 2006 Dec;12(10):1035-9.

Williams DA, Gracely RH. Biology and therapy of fibromyalgia. Functional magnetic resonance imaging findings in fibromyalgia. Arthritis Res Ther. 2006;8(6):224.

ARTHRITIS & RHEUMATISM
Vol. 54, No. 11, November 2006, pp 3494–3507
DOI 10.1002/art.22160

Risedronate Decreases Biochemical Markers of Cartilage Degradation but Does Not Decrease Symptoms or Slow Radiographic Progression in Patients With Medial Compartment Osteoarthritis of the Knee

Results of the Two-Year Multinational Knee Osteoarthritis Structural Arthritis Study

Clifton O. Bingham, III,[1] J. Chris Buckland-Wright,[2] Patrick Garnero,[3] Stanley B. Cohen,[4] Maxime Dougados,[5] Silvano Adami,[6] Daniel J. Clauw,[7] Timothy D. Spector,[8] Jean-Pierre Pelletier,[9] Jean-Pierre Raynauld,[9] Vibeke Strand,[10] Lee S. Simon,[11] Joan M. Meyer,[12] Gary A. Cline,[12] and John F. Beary[12]

Objective. **Bisphosphonates have slowed the progression of osteoarthritis (OA) in animal models and have decreased pain in states of high bone turnover. The Knee OA Structural Arthritis (KOSTAR) study, which is the largest study to date investigating a potential structure-modifying OA drug, tested the efficacy of risedronate in providing symptom relief and slowing disease progression in patients with knee OA.**

Methods. **The study group comprised 2,483 patients with medial compartment knee OA and 2–4 mm of joint space width (JSW), as determined using fluoroscopically positioned, semiflexed-view radiography. Patients were enrolled in 2 parallel 2-year studies in North America and the European Union. These studies evaluated the efficacy of risedronate at dosages of 5 mg/day, 15 mg/day, 35 mg/week (in Europe), and 50 mg/week (in North America) compared with placebo in reducing signs and symptoms, as measured by the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index and patient global assessment (PGA) scores, and in slowing radiographic progression.**

Results. **A reduction of ~20% in signs and symptoms, as measured by WOMAC subscales and PGA scores, was observed in all groups, with no treatment effect of risedronate demonstrated. Risedronate did not**

[1]Clifton O. Bingham, III, MD: Johns Hopkins University, Baltimore, Maryland; [2]J. Chris Buckland-Wright, PhD, DSc: King's College, London, UK; [3]Patrick Garnero, PhD: INSERM Research Unit 664, and Synarc, Lyon, France; [4]Stanley B. Cohen, MD: St. Paul Medical Center, Dallas, Texas; [5]Maxime Dougados, MD: Hôpital Cochin, Paris, France; [6]Silvano Adami, MD: University of Verona, Verona, Italy; [7]Daniel J. Clauw, MD: University of Michigan, Ann Arbor; [8]Timothy D. Spector, MD, MSc, FRCP: St. Thomas Hospital, London, UK; [9]Jean-Pierre Pelletier, MD, Jean-Pierre Raynauld, MD, FRCPC: Centre Hospitalier de l'Université de Montréal, Hôpital Notre-Dame, Montréal, Québec, Canada; [10]Vibeke Strand, MD: Stanford University School of Medicine, Palo Alto, California; [11]Lee S. Simon, MD: Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, Massachussetts; [12]Joan M. Meyer, PhD, Gary A. Cline, PhD, John F. Beary, MD: Procter & Gamble Pharmaceuticals, Mason, Ohio.

Dr. Bingham has received consulting fees (less than $10,000) from Procter & Gamble. Dr. Cohen has received consulting fees and/or honoraria (less than $10,000) from Procter & Gamble. Dr. Dougados has received consulting fees and/or honoraria (less than $10,000) from Procter & Gamble. Dr. Adami has received consulting fees and/or honoraria (less than $10,000) from Procter & Gamble. Dr. Spector has received consulting fees and/or honoraria (more than $10,000) from Procter & Gamble. Dr. Strand has served as a consultant to and/or has received honoraria (less than $10,000 each) from Abbott Immunology, Amgen, Biogen Idec, Can-Fite BioPharma Ltd., Celera, Centocor, Chelsea Therapeutics, Coley Pharmaceutical Group, Cypress Pharmaceutical, FibroGen, Genelabs Technologies, Genentech, Human Genome Sciences, Immunomedics, Incyte Pharmaceuticals, Millennium Pharmaceuticals, Novartis, Omeros, Pfizer, Procter & Gamble, Rigel Pharmaceuticals, Roche, Sanofi Aventis, Schering-Plough, Scios, Serono, Sanwa Kagaku Kenkyusho Ltd., Sumitomo, UCB Pharma, XDx, and Xencor. Additionally, Dr. Strand serves on advisory boards for Abbott Immunology, Alder Biopharmaceuticals, Amgen, BioSeek, CanFite BioPharma, Centocor, Chelsea Therapeutics, Jazz Pharmaceuticals, Novartis, Pfizer, Robert Wood Johnson Pharmaceutical Research Institute, Roche, Sanofi-Aventis, Savient Pharmaceuticals, UCB Pharma, and Wyeth, and serves on speaking bureaus for Abbott Immunology, Amgen, Centocor, Novartis, Pfizer, and Santofi-Adventis.

Address correspondence and reprint requests to Clifton O. Bingham, III, MD, Divisions of Rheumatology and Allergy and Clinical Immunology, Johns Hopkins University, 5200 Eastern Avenue, Mason F. Lord Building, Center Tower, Room 404, Baltimore, MD 21224. E-mail: Clifton.bingham@jhmi.edu.

Submitted for publication January 31, 2006; accepted in revised form July 11, 2006.

significantly reduce radiographic progression as measured by decreased JSW or using a dichotomous definition of progression (joint space loss of ≥0.6 mm). Thirteen percent of patients receiving placebo demonstrated significant disease progression over 2 years. A dose-dependent reduction in the level of C-terminal crosslinking telopeptide of type II collagen, a cartilage degradation marker associated with progressive OA, was seen in patients who received risedronate. No increase in the number of adverse events was demonstrated for risedronate compared with placebo.

***Conclusion*. Although risedronate (compared with placebo) did not improve signs or symptoms of OA, nor did it alter progression of OA, a reduction in the level of a marker of cartilage degradation was observed. A sustained clinically relevant improvement in signs and symptoms was observed in all treatment and placebo groups.**

Osteoarthritis (OA) is the most prevalent form of arthritis, affecting more than 10% of the population and an estimated 21 million adults in the US (1). The disease is associated with significant pain and disability and is a major factor necessitating hip or knee replacement. OA is characterized by focal cartilage loss, subchondral bony changes, osteophyte formation, and (in some cases) synovitis with involvement of periarticular structures. Most pharmacologic therapy for OA is directed toward symptom control, using analgesics, nonsteroidal antiinflammatory drugs (NSAIDs), and cyclooxygenase 2 (COX-2) inhibitors. Weight loss, physical therapy, and activity are also important components of treatment. To date, there has been limited evidence for therapies that slow the disease process. Although glucosamine has been advocated as a possible structure-modifying OA drug (SMOAD) (2), data are inconsistent, and questions remain as to its absorption and putative action (3,4). Recent data have suggested a possible benefit of doxycycline in slowing radiographic progression (but not altering symptoms) in obese women with knee OA (5). Treatment with diacerein slowed radiographic progression in patients with hip OA over 3 years but had no effect on signs and symptoms (6,7). Evaluating drugs as potential SMOADs presents significant challenges for developing appropriate study designs and outcomes.

Failure of the OA joint represents cartilage degradation but may also reflect changes in subchondral bone, with decreased numbers and thinning of tibial cancellous trabeculae and localized subchondral osteoporosis in knee OA (8–10), confirming earlier observations of periarticular osteoporosis in some patients (11). Subchondral bone lesions, which are seen by magnetic resonance imaging (MRI) in many patients with OA, may represent histologic microfractures (12–14). In the Duncan-Hartley guinea pig model of spontaneous OA, subchondral bony changes are a characteristic of the disease process (15), and risedronate inhibited histologic disease progression, with a 30–40% reduction in cartilage damage (16–18). Bisphosphonates have also been effective in slowing disease progression in other animal models of OA (19,20).

Agents that suppress bone turnover, including bisphosphonates, have been associated with fewer subchondral bony lesions (as visualized by MRI) in patients with OA (21); such lesions are independently correlated with levels of pain and disease progression (22). Levels of bone turnover markers are higher in patients with progressive OA and are similar to those in patients with postmenopausal osteoporosis (23). Data from trials of patients with Paget's disease indicated that short treatment courses of higher-dosage risedronate (30 mg/day) improved bone lesions, reduced biochemical indices of disease activity (24), and reduced bone pain (25–27). In a 1-year study, 285 patients with knee OA received risedronate at a dosage of 5 mg/day, risedronate at a dosage of 15 mg/day, or placebo (28). A consistent trend for pain reduction with the highest dosage of risedronate was observed at 6 months, and a consistent trend for statistically significantly different responses in patient global assessment of disease (PGA) scores was observed at 1 year. Although these differences suggested a possible benefit in retarding radiographic progression, with 1% of patients in the group receiving risedronate at a dosage of 15 mg/day showing disease progression (≥0.75-mm joint space loss) over 1 year compared with 8% of patients in the placebo group, the differences were not statistically significant. A dose-dependent reduction in the level of urinary C-terminal crosslinking telopeptide of type II collagen (CTX-II) was also observed in that study. Thus, there is rationale for suggesting that a bisphosphonate, potentially acting to inhibit bone turnover, may have a role in the treatment of OA.

Risedronate, a pyridinyl bisphosphonate that decreases bone resorption and turnover, is efficacious for postmenopausal and corticosteroid-induced osteoporosis and, in higher doses, for Paget's disease of bone (26,27,29,30). We explored the efficacy of risedronate, in a range of doses, in knee OA.

PATIENTS AND METHODS

Study design. Two parallel phase III studies were conducted in North American and European Union sites, respectively. These were 2-year, multicenter, randomized, double-blind, placebo-controlled studies of oral risedronate at dosages of 5 mg/day, 15 mg/day, and 35 mg/week (European sites) or 5 mg/day, 15 mg/day, and 50 mg/week (North American sites) in patients with medial compartment knee OA. The studies were conducted in 42 centers in North America (US and Canada) and in 44 European centers (11 countries). All patients provided written informed consent before entering the study, which was conducted in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines for Good Clinical Practice and was administered by local and central institutional review boards.

Male and female patients, ages 40–80 years (inclusive), were recruited. Patients who underwent screening had signal knee pain due to OA on most days during at least 1 month in a 3-month period prior to screening, plus at least 1 of the following: age >50 years, morning knee stiffness lasting <30 minutes, or knee crepitus according to the American College of Rheumatology (formerly, the American Rheumatism Association) criteria for knee OA (31). All patients then underwent radiography of the knee, to confirm the presence of OA. A specified minimum or maximum level of background pain was not required for inclusion in the study.

Major exclusions were the following: known inflammatory arthritis, body mass index (BMI) >40 kg/m^2, cancer within 10 years, tetracycline use within 6 months, intraarticular injection of corticosteroids or hyaluronan preparations within 3 months, calcitonin or fluoride use within 6 months, and prior use of bisphosphonates within 12 months or for >60 days ever.

To determine whether patients had a qualifying knee radiograph, standardized radiography with fluoroscopically positioned semiflexed anteroposterior (AP) views was used. The SD for this technique was ~0.2 mm for radiographs obtained 2 days apart, based on repeat measurements (32). At least 1 osteophyte and minimal joint space width (JSW) of 2–4 mm, inclusive, in the medial tibiofemoral compartment, and a medial compartment that was narrower than the lateral were required. If both knees qualified, the signal knee was defined as the knee with the smaller JSW. Radiographic assessments were conducted at baseline, 1 year, and 2 years. Patients who withdrew were asked to return for the 24-month assessment, which included radiography.

Treatment assignment. Equal proportions of North American patients were assigned to receive either placebo, risedronate 5 mg/day, risedronate 15 mg/day, or risedronate 50 mg/week. Equal proportions of European patients were assigned to receive either placebo, risedronate 5 mg/day, risedronate 15 mg/day, or risedronate 35 mg/week. At each center, patients were randomized to treatment groups and stratified according to current use of estrogens/selective estrogen receptor modulators (SERMs).

Patients were instructed to take the study drug with sufficient plain water, once daily while in an upright position, with an empty stomach in the morning at least 30 minutes before eating or drinking anything, or, at other times during the day, at least 2 hours before or after eating or drinking and not less than 30 minutes before bedtime.

The dosages of risedronate used in these studies were based on the dosage used for postmenopausal osteoporosis (5 mg/day) and a daily dose of 15 mg, which was believed to clearly separate from the 5 mg/day dosage with regard to serum concentrations. The weekly dosing groups (35 mg/week in Europeans and 50 mg/week in North Americans) were included to provide the opportunity to evaluate the efficacy of a more convenient weekly dosing regimen, with the 50 mg/week dosage chosen to provide information regarding an intermediate total weekly dose.

Background analgesics and stepped reduction. Nonnarcotic analgesics, NSAIDs, or COX-2 inhibitors were permitted and monitored, with changes according to physician preference and clinical course. All patients underwent a stepped analgesic reduction and washout period before study visits, including the baseline visit. Each patient was provided with acetaminophen (North America)/paracetamol (Europe) (500 mg) and diclofenac (50 mg), to be used as needed as the only pain medications from day −5 to day −3 preceding the baseline, 6-, 12-, 18-, and 24-month visits. All pain medications were discontinued on day −2 and day −1 prior to these visits and on the visit day. WOMAC and PGA questions referred to the preceding 48 hours.

Treatment outcomes. The coprimary efficacy objectives were to assess the effect of risedronate on structure and symptoms in patients with mild to moderate knee OA relative to placebo. OA symptoms were measured by the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index (33) and by PGA scores. WOMAC measurements were collected on a 100-mm visual analog scale. Questionnaires and assessment instruments in the local languages were provided to the investigative sites. Standardized training was provided at investigator meetings in North America and Europe and was monitored throughout the study.

The average values for each domain were calculated and reported at each time point. The total WOMAC score was calculated as the sum of individual measurements divided by the total number of questions. Structure was assessed by measuring the progression of joint space narrowing (JSN) in the medial tibiofemoral compartment in the pooled North American and European studies after 2 years.

Radiographic assessment. The JSW of the target knee was evaluated at baseline and after 1 and 2 years of followup, at the narrowest point in the medial tibiofemoral compartment (32,34,35). This protocol standardized radiographs with a semiflexed view of the knee, aided by fluoroscopy, and by attaching a metal sphere to the fibula head to correct magnification effects. Minimum medial compartment JSW was measured with a semiautomated computerized method.

To ensure proper quality, exposure, positioning of the knee joint, and reproducibility of the JSW measurements, radiographs were obtained at 13 regional radiographic facilities (RRFs) in Europe and 12 RRFs in the US, by specially trained personnel (32); quality, exposure, positioning, and acceptability were checked on an ongoing basis. A standing AP fluoroscopically assisted semiflexed view of the signal knee was obtained according to the procedure described by Buckland-Wright and was shown to be accurate and reproducible (34,35). Each knee was flexed until the tibial plateau was horizontal

relative to the floor, parallel to the central x-ray beam and perpendicular to the radiograph film. The center of the joint, defined by the joint space, was aligned with the center of the x-ray beam with the aid of the tube's positioning light.

The precise knee position was obtained visually with the aid of fluoroscopy. With the heel fixed, the foot was internally or externally rotated until the tibial spines appeared centrally placed relative to the femoral notch; then, the knee was flexed to achieve superimposition ($\pm$1 mm) of the anterior and posterior margins of the medial tibial plateau. All radiographs were sent to the Radiographic Quality Control Centre (RQCC) in Amsterdam, The Netherlands (European patients) or to the RQCC in Ann Arbor, Michigan (North American patients), where radiographs had to pass strict quality control measures, and then on to the Central Analysis Facility at King's College in London, where the films were digitized, and semiautomated computerized measurements of minimal medial JSW were performed. This is a highly reproducible image analysis technique. For this technique, the test–retest SD for the difference between radiographs obtained 2 days apart was ~0.2 mm. The coefficient of variation for the reproducibility of the software to measure medial compartment JSW had been determined previously as 1% for test–retest radiographs of the knee in the semiflexed position (34).

Osteophytes were assessed manually on temporally ordered films by 2 radiologists and scored (if present) on the medial tibial edge, the lateral tibial edge, or the tibial spine. Baseline and exit films were graded according to the Osteoarthritis Research Society International osteophyte grading conventions on a 0–3 scale, using a reference manual (36). The percent change in osteophyte size relative to baseline was also graded, as follows: 0 = no definite growth, 1 = <50% growth, 2 = growth >50% and <100%, 3 = >100% growth. In a small validation substudy of the percent change in osteophyte size parameter, the percent of exact matches of osteophyte scores ranged from 87–97% for intrareader agreement and 74–95% for interreader agreement.

Safety ssessments. Safety data, including physical examination, vital signs, laboratory evaluations, concomitant medications, and adverse events, were collected from all patients every 3 months. Adverse events were coded according to COSTART (Coding Symbols for a Thesaurus of Adverse Reaction Terms) definitions, with severity and attributability recorded.

Assessment of biochemical markers. Early-morning, fasting, second-void urine samples were collected at baseline and at the month 6, month 12, and month 24 (exit) visits, to measure bone and cartilage turnover. Samples were frozen and analyzed in bulk. Bone resorption was assessed by determining urine levels of N-terminal crosslinking telopeptide of type I collagen (NTX-I) (Osteomark; OrthoClinical Diagnostics, Rochester, NY), and cartilage degradation was assessed with urine levels of CTX-II (CartiLaps; Nordic Bioscience, Herlev, Denmark). The detection limits of the assays were as follows: for NTX-I, 4 nmoles of BCE/liter; for CTX-II, 0.25 μg/liter. The urinary CTX-II assay is based on a mouse monoclonal antibody raised against the EKGPDP sequence of human type II collagen C-telopeptide, a sequence observed exclusively in type II collagen and not in the other collagens, including type I, or other structural proteins. The antibody has no significant cross-reactivity with type I collagen C-telopeptide (37). Interassay variability and intraassay variability were lower than 10% for both assays. Levels of urinary creatinine were measured for marker normalization.

Sample size and data analysis plans. Each study was initially designed to assure 90% power to detect a 40% protective effect of risedronate versus placebo in reducing JSN, assuming a 0.2-mm/year rate of JSN in the placebo population, a SD of 0.45 mm, a 2-year dropout rate of 30%, and a Type I error rate of 5% with Dunnett's adjustment for multiple-dose 2-sided comparisons with placebo, with a sample size requirement of 302 patients per treatment group. The study was sized for 90% power to detect a mean 0.16-mm JSN difference between a placebo-treated and a risedronate-treated group.

Prior to unblinding, it was determined that the mean rate of radiographic progression among patients receiving placebo was expected to be ~0.085 mm per year, based on the results of a smaller study using the same radiographic techniques (28), rather than a rate of 0.20 mm per year, as originally expected. As a result, the protocols were modified to focus on a pooled JSW analysis from the combined North American and European studies as the primary structure end point to provide 90% power for a 50% relative risk reduction, with a placebo-associated progression rate of 14%. The statistical analysis plan specified that the primary JSW analysis was to compare the mean JSN that occurred with placebo, provided analysis of variance (ANOVA) assumptions were met. If ANOVA assumptions were not met, the primary structure was to be the proportion of patients in whom disease progressed (defined as JSW loss of $\geq$0.6 mm across treatment groups), representing 3 times the SD of the measurement (32), which was the case for the final analysis.

The first planned primary analysis was a comparison of the month 24 mean change from baseline in the total WOMAC score between patients receiving the highest dosage of risedronate (15 mg/day) and patients receiving placebo, within each study. If the total WOMAC score at month 24 was statistically significant for the group receiving risedronate at a dosage of 15 mg/day versus the placebo group, then the pooled study JSW and within-study PGA analyses would simultaneously be conducted to compare the group receiving 15 mg/day of risedronate with the placebo group, using a step-down approach. Sign and symptom end points were evaluated by study (North America or Europe); however, the analyses of structure examined patients in the different dose groups, pooled for the studies.

The primary analysis of mean JSW was adjusted at each time point by using the study (North America/European Union), baseline use of estrogen/SERMs, sex, age, BMI, and baseline JSW as covariates. The JSW progressor analysis used the Cochran-Mantel-Haenszel test, with the North American study and the European study as strata. Symptom analyses at each time point were adjusted by using the appropriate baseline total WOMAC score or PGA value, pooled centers, baseline use of estrogen/SERMs, sex, age, BMI, and baseline JSW as covariates. Mean changes from baseline in measures of signs and symptoms were evaluated using repeated-measures analysis adjusted for pooled centers, baseline PGA score, baseline use of estrogen/SERMs, sex, age, BMI, and baseline JSW. The ANOVA model was used for primary symptom

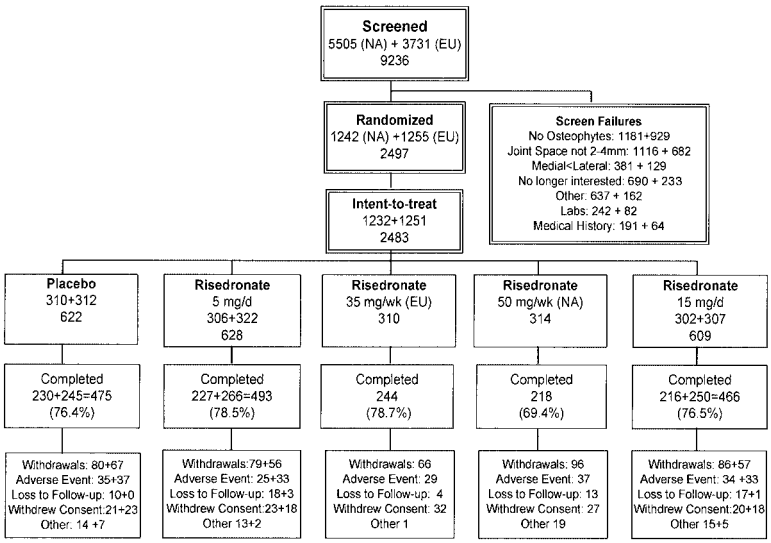


Figure 1. Flow chart of the study. Patients who continued to receive study medication through month 24 are indicated as completers. NA = North America; EU = European Union.

Table 1. Baseline characteristics of patients in the North American cohort*

Characteristic	Placebo (n = 310)	Risedronate, 5 mg/day (n = 306)	Risedronate, 15 mg/day (n = 302)	Risedronate, 50 mg/week (n = 314)	*P*	Total (n = 1,232)
Age, years	60.2 ± 0.51	60.6 ± 0.51	60.4 ± 0.51	60.7 ± 0.49	0.9125	60.5 ± 0.25
Female sex, no. (%)	178 (57)	189 (62)	196 (65)	194 (62)	0.2992	757 (61)
Race, no. (%)						
Asian	6 (2)	3 (1)	4 (1)	7 (2)		20 (2)
Black	27 (9)	28 (9)	33 (11)	21 (7)		109 (9)
Hispanic	11 (4)	10 (3)	11 (4)	11 (4)		43 (3)
Other	1 (<1)	7 (2)	6 (2)	5 (2)		19 (2)
White	265 (85)	258 (84)	248 (82)	270 (86)	0.6261	1,041 (84)
Height, cm	169.0 ± 0.59	168.5 ± 0.54	168.4 ± 0.58	167.7 ± 0.56	0.4677	168.4 ± 0.28
Weight, kg	87.0 ± 0.96	86.0 ± 0.90	85.0 ± 0.96	86.6 ± 0.93	0.4708	86.2 ± 0.47
Body mass index, kg/m^2	30.4 ± 0.28	30.2 ± 0.27	29.9 ± 0.27	30.7 ± 0.27	0.2018	30.3 ± 0.14
Postmenopausal, no. (%)†	130 (73)	148 (78)	141 (72)	150 (77)	0.4485	569 (75)
Estrogen/SERM use, no. (%)†	87 (49)	83 (44)	75 (38)	90 (46)	0.1903	335 (44)
WOMAC total score	39.7 ± 1.29	41.0 ± 1.27	39.6 ± 1.29	40.6 ± 1.31	0.8263	40.2 ± 0.65
WOMAC pain score	36.4 ± 1.24	37.8 ± 1.23	37.1 ± 1.27	37.6 ± 1.32	0.8546	37.2 ± 0.63
WOMAC function score	39.8 ± 1.36	41.3 ± 1.34	39.6 ± 1.36	40.9 ± 1.36	0.7733	40.4 ± 0.67
WOMAC stiffness score	45.9 ± 1.45	46.9 ± 1.48	45.4 ± 1.52	45.9 ± 1.52	0.9198	46.0 ± 0.75
Patient global assessment score	52.6 ± 1.38	52.8 ± 1.40	51.4 ± 1.39	54.2 ± 1.44	0.5627	52.8 ± 0.70
Joint space width, mm	2.947 ± 0.0335	2.970 ± 0.0346	2.979 ± 0.0341	2.997 ± 0.0335	0.7626	2.973 ± 0.0170
NSAID use, no. (%)	228 (74)	235 (77)	208 (69)	216 (69)	0.0742	887 (72)
Celecoxib use, no. (%)	53 (17)	48 (16)	54 (18)	52 (17)	0.9064	207 (17)
Rofecoxib use, no. (%)	42 (14)	53 (17)	33 (11)	40 (13)	0.1313	168 (14)
Acetaminophen use, no. (%)	138 (45)	140 (46)	145 (48)	136 (43)	0.6830	559 (45)
Glucosamine/chondroitin use, no. (%)	92 (30)	77 (25)	76 (25)	87 (28)	0.5227	332 (27)
NTX-I/Cr, nmole BCE/nmole Cr	37.48 ± 1.964	36.27 ± 1.001	38.80 ± 1.072	37.62 ± 1.009	0.6182	37.54 ± 0.662
CTX-II/Cr, ng/nmole Cr	296.47 ± 17.087	273.48 ± 10.682	297.16 ± 14.872	273.02 ± 9.637	0.3765	284.93 ± 6.690

* Except where indicated otherwise, values are the mean ± SEM. *P* values indicate differences across treatment groups. The chi-square test was used to compare categorical variables, and analysis of variance was used to compare continuous variables. SERM = selective estrogen receptor modulator; WOMAC = Western Ontario and McMaster Universities Osteoarthritis index; NSAID = nonsteroidal antiinflammatory drug; NTX-I = N-terminal crosslinking telopeptide of type I collagen; Cr = creatinine; CTX-II = urinary C-terminal crosslinking telopeptide of type II collagen.
† Female patients only.

Table 2. Baseline characteristics of patients in the European Union (EU) cohort*

Parameter	Placebo (n = 312)	Risedronate, 5 mg/day (n = 322)	Risedronate, 15 mg/day (n = 307)	Risedronate, 35 mg/week (n = 310)	*P*†	Total (n = 1,251)	*P*, NA vs. EU‡
Age, years	63.6 ± 0.48	63.7 ± 0.45	62.9 ± 0.47	64.1 ± 0.48	0.2901	63.6 ± 0.23	<0.0001
Female sex, no. (%)	259 (83)	254 (79)	235 (77)	243 (78)	0.2395	991 (79)	<0.0001
Race, no. (%)							
Asian	3 (1)	1 (<1)	1 (<1)	1 (<1)		6 (<1)	
Black	1 (<1)	3 (1)	2 (1)	0 (0)		6 (<1)	
Hispanic	0 (0)	0 (0)	0 (0)	1 (<1)		1 (<1)	
Other	10 (3)	10 (3)	9 (3)	14 (5)		43 (<3)	
White	298 (96)	308 (96)	295 (96)	294 (95)	0.6407	1,195 (96)	<0.0001
Height, cm	164.4 ± 0.45	164.6 ± 0.46	164.6 ± 0.49	164.6 ± 0.48	0.9799	164.5 ± 0.23	<0.0001
Weight, kg	79.8 ± 0.72	79.3 ± 0.66	79.6 ± 0.69	79.1 ± 0.72	0.9230	79.4 ± 0.35	<0.0001
Body mass index, kg/m^2	29.5 ± 0.24	29.3 ± 0.24	29.4 ± 0.23	29.2 ± 0.24	0.8494	29.4 ± 0.12	<0.0001
Postmenopausal, no. (%)§	244 (94)	240 (94)	213 (91)	222 (91)	0.4773	919 (93)	<0.0001
Estrogen/SERM use, no. (%)§	29 (11)	31 (12)	27 (11)	35 (14)	0.6979	122 (12)	<0.0001
WOMAC total score	47.0 ± 1.16	44.5 ± 1.16	47.1 ± 1.17	44.6 ± 1.21	0.2156	45.8 ± 0.59	<0.0001
WOMAC pain score	43.7 ± 1.20	40.8 ± 1.18	44.3 ± 1.19	41.0 ± 1.23	0.0766	42.4 ± 0.60	<0.0001
WOMAC function score	48.0 ± 1.23	45.5 ± 1.23	47.9 ± 1.24	45.7 ± 1.27	0.3108	46.8 ± 0.62	<0.0001
WOMAC stiffness score	47.4 ± 1.51	45.8 ± 1.40	47.1 ± 1.44	44.2 ± 1.53	0.4089	46.1 ± 0.74	0.9444
Patient global assessment score	56.9 ± 1.27	55.0 ± 1.29	56.2 ± 1.34	57.1 ± 1.30	0.6510	56.3 ± 0.65	0.0002
Joint space width, mm	2.976 ± 0.0345	2.991 ± 0.0346	2.955 ± 0.0309	2.963 ± 0.0337	0.8798	2.971 ± 0.0167	0.9405
NSAID use, no. (%)	175 (56)	193 (60)	180 (59)	170 (55)	0.5541	718 (57)	<0.0001
Celecoxib use, no. (%)	5 (2)	4 (1)	3 (1)	5 (2)	0.8840	17 (8)	<0.0001
Rofecoxib use, no. (%)	6 (2)	2 (1)	6 (2)	12 (4)	0.0399	26 (2)	<0.0001
Acetaminophen use, no. (%)	79 (25)	97 (30)	83 (27)	82 (26)	0.5654	341 (27)	<0.0001
Glucosamine/chondroitin use, no. (%)	25 (8)	26 (8)	24 (8)	25 (8)	0.9994	100 (8)	<0.0001
NTX-I/Cr, nmole BCE/nmole Cr	49.43 ± 1.364	46.79 ± 1.307	49.91 ± 2.097	46.20 ± 1.241	0.2238	48.07 ± 0.768	<0.0001
CTX-II/Cr, ng/nmole Cr	376.72 ± 13.724	367.17 ± 13.664	360.70 ± 12.059	361.71 ± 16.798	0.8498	366.58 ± 7.080	<0.0001

* Except where indicated otherwise, values are the mean ± SEM. The chi-square test was used to compare categorical variables, and analysis of variance was used to compare continuous variables. NA = North America (see Table 1 for other definitions).
† Differences across treatment groups.
‡ By Fisher's exact test for categorical variables and by analysis of variance for continuous variables.
§ Female patients only.

analyses. Unless noted otherwise, all statistical analyses were 2-sided, with a Type I error rate of 0.05.

The primary analyses were modified intent-to-treat (ITT) analyses conducted using data from all randomized patients who received at least 1 dose of study drug. In these ITT analyses, data for some patients may have been missing, due to missed visits, withdrawal, or other reasons. Missing data were not imputed for the primary efficacy end points. A per-protocol analysis for each efficacy end point was conducted for patients who met all protocol inclusion/exclusion criteria, who were compliant (taking at least 75% of the study drug), and who had no other major deviations.

RESULTS

A total of 9,236 patients at 42 sites in North America (US and Canada) and at 44 centers in Europe were screened for participation in the KOSTAR study. The most common factors involved in screening failure were radiographic criteria, including lack of qualifying osteophytes and JSW >4 mm or <2 mm. A total of 2,497 patients were randomized, and 2,483 were enrolled, constituting the ITT population, with 1,232 patients in the North American cohort and 1,251 patients in the European cohort (Figure 1). The overall screening-to-randomization ratio was ~4:1. Overall patient retention was very high, with 86.7% of patients completing the final visit at 2 years, and 76.4% completing the study without dropping out. The percentage of withdrawals in North America (27.7%) was greater than that in Europe (19.7%), largely because of loss to followup. The numbers of patients who withdrew due to adverse events were similar across groups. No differences in the number of withdrawals were noted in either study (North America or Europe), across treatment groups or in combined studies.

Several differences in the clinical characteristics of randomized patients in the North American and European studies were noted (Tables 1 and 2). The North American study population included more men, and the average age of North American patients was

Table 3. Changes in WOMAC and PGA scores from baseline to month 24 among patients in the North American and European cohorts*

		Risedronate			
	Placebo	5 mg/day	35 mg/week	50 mg/week	15 mg/day
North America					
WOMAC total	−9.5 ± 1.31	−7.9 ± 1.34	–	−10.8 ± 1.33	−8.2 ± 1.38
WOMAC pain	−8.4 ± 1.34	−8.2 ± 1.39	–	−9.9 ± 1.38	−7.9 ± 1.42
WOMAC function	−9.3 ± 1.33	−7.7 ± 1.37	–	−10.7 ± 1.36	−7.8 ± 1.41
WOMAC stiffness	−11.9 ± 1.59	−9.9 ± 1.65	–	−13.6 ± 1.63	−12.0 ± 1.69
PGA	−8.7 ± 1.71	−8.5 ± 1.77	–	−10.8 ± 1.75	−7.6 ± 1.82
European Union					
WOMAC total	−10.0 ± 1.63	−11.2 ± 1.58	−11.6 ± 1.60	–	−11.7 ± 1.62
WOMAC pain	−10.1 ± 1.71	−11.4 ± 1.66	−12.1 ± 1.67	–	−12.3 ± 1.70
WOMAC function	−9.9 ± 1.68	−11.0 ± 1.63	−11.6 ± 1.65	–	−11.5 ± 1.66
WOMAC stiffness	−10.5 ± 1.93	−13.9 ± 1.86	−12.3 ± 1.88	–	−12.8 ± 1.91
PGA	−15.6 ± 2.13	−15.2 ± 2.06	−17.0 ± 2.08	–	−17.2 ± 2.12

* Values are the adjusted mean ± SEM. The symptom analyses at each time point were adjusted using the appropriate baseline Western Ontario and McMaster Universities Osteoarthritis index (WOMAC) total score or patient global assessment (PGA) score, pooled centers, baseline use of estrogens or selective estrogen receptor modulators, sex, age, body mass index, and baseline joint space width as covariates.

younger (60.5 years versus 63.6 years in the European study). Although more European women were postmenopausal, more women in the North American group took estrogen or SERMs. Patients in North America were heavier, with a higher mean BMI (30.3 kg/m^2 versus 29.4 kg/m^2). The baseline total WOMAC scores, scores for all WOMAC domains, and PGA scores were higher in Europeans, although WOMAC scores for stiffness were not significantly different ($P = 0.944$). More patients in North America were taking NSAIDS and coxibs as analgesics. The baseline characteristics were, however, comparable across the different treatment groups within each study. The mean JSWs at baseline in the North American and European studies were not significantly different ($P = 0.9405$), reflecting standardized radiographic methods and the requirements for study entry.

Signs and symptoms. In both the European and North American studies, no significant differences between treatment groups were noted in the mean change from baseline in total WOMAC score, scores for WOMAC components, or PGA scores (Table 3). In the placebo-treated group, a reduction of ~20% from baseline was seen in total WOMAC scores as well as in each subcomponent. No statistically significant differences or trends were noted for any dose of risedronate. Similarly, the reduction in PGA scores was of a similar magnitude across all 5 treatment groups. Although the baseline and final WOMAC scores, subscale scores, and PGA scores were higher in the European group than in the North American group, the reductions from baseline were similar. Reductions were seen at the first time point (6 months) and were maintained throughout 2 years in all groups (Figure 2). There was a reduction in the average number of days and number of pills of analgesic medi-

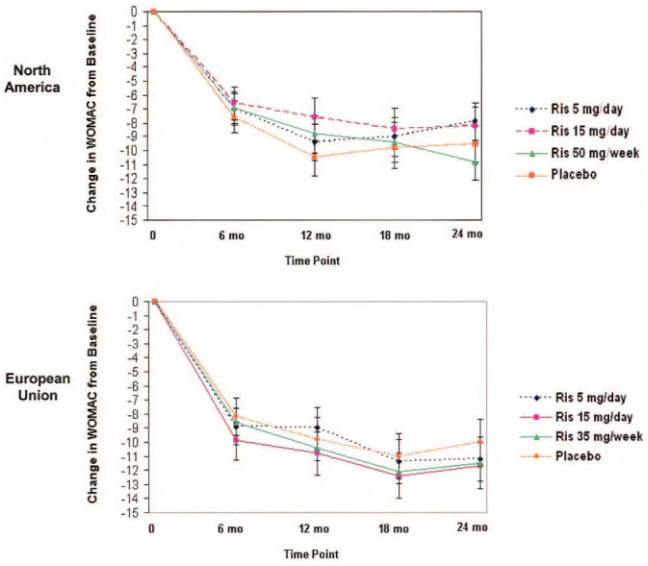


Figure 2. Adjusted mean ± SEM changes from baseline in total Western Ontario and McMaster Universities Osteoarthritis (WOMAC) and WOMAC pain subscale scores over 24 months. The symptom analyses at each time point were adjusted using the appropriate baseline WOMAC score, pooled centers, baseline use of estrogen or selective estrogen receptor modulators, sex, age, body mass index, and baseline joint space width as covariates. Ris = risedronate.

Table 4. Proportion of patients experiencing radiographic progression, defined as ≥0.6 mm of JSN over 24 months*

	Placebo	Risedronate, 5 mg/day	Risedronate, 35 mg/week	Risedronate, 50 mg/week	Risedronate, 15 mg/day	Total
North America						
No. of radiographs	269	268		268	260	1,065
No. (%) progressors	37 (14)	43 (16)		38 (14)	36 (14)	154 (14)
European Union						
No. of radiographs	280	305	280		283	1,148
No. (%) progressors	35 (13)	35 (11)	31 (11)		39 (14)	140 (12)
Combined total						
No. of radiographs	549	573	280	268	543	2,213
No. (%) progressors	72 (13)	78 (14)	31 (11)	38 (14)	75 (14)	294 (13)

* The narrowest medial compartment joint space width (JSW) was measured using standardized fluoroscopically positioned semiflexed-view knee radiographs obtained at baseline, 12 months, and 24 months, in the North American, European, or combined studies. A patient was defined as a progressor using a dichotomous definition of a ≥0.6 mm decrease in JSW from baseline at any postbaseline measurement. JSN = joint space narrowing.

cation taken per week in the placebo group and all treatment groups in North America and Europe, with no differences noted with any risedronate dose compared with placebo (data not shown).

Radiographic changes. Because in the combined symptomatic analysis of 15 mg/day of risedronate versus placebo, ANOVA assumptions were not met using the prespecified definitions, the primary analysis for structure modification was performed using JSW progression as the end point. The proportion of patients experiencing radiographic progression, defined as ≥0.6 mm of JSN over 24 months, was 13% overall, with no statistically significant differences noted in any treatment group or in the North American versus European cohorts (Table 4). Although the proportion of JSW progressors was small at 2 years, it was similar to that extrapolated based on progression among patients receiving placebo in the pilot study (31) on which this analysis was modeled.

Most patients had no radiographic worsening, defined as JSN of ≥0.6 mm. An approximate normal distribution within 3 SD of the measurement error was observed (Figure 3). Although a few patients could be classified as having joint space "improvement," this is most likely attributable to expected measurement error in joint space over 2 years. Far more patients were represented within the progression "tail," with many progressors demonstrating marked loss of joint space of >1 mm and sometimes >2 mm.

The observed mean ± SD reductions in JSW in the placebo groups over 24 months were 0.088 ± 0.040 mm in the European cohort and 0.130 ± 0.033 mm in the North American cohort. No statistically significant differences were noted for any dose of risedronate compared with placebo, for either study or for the combined data (data not shown). Although in this study, changes in grading according to the Kellgren/Lawrence scale (38) were not specifically evaluated, there was no difference between treatment groups in medial, lateral, or tibial spine osteophyte changes at 2 years. In the different treatment groups, 26–37% of patients had worsening of medial spine osteophytes, 10–22% had worsening of lateral spine osteophytes, and 3–19% had worsening of tibial spine osteophytes, with no group demonstrating trends or statistically significant differences compared with placebo (data not shown).

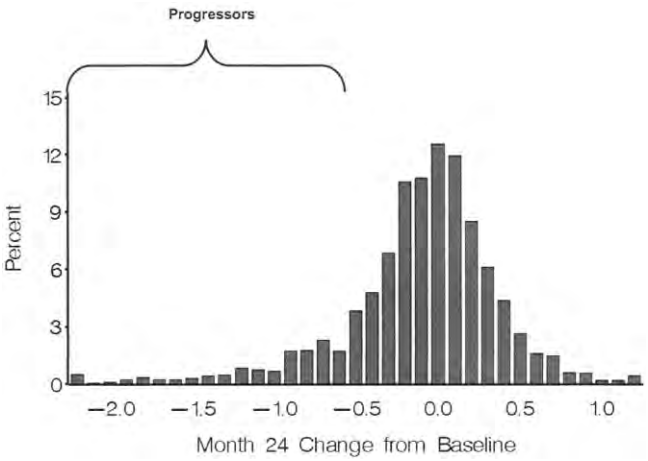


Figure 3. Histogram showing the percent change from baseline in joint space width (JSW) among patients defined as progressors, in the combined North American and European studies. The narrowest JSW in the medial compartment was measured using an automated method of digitized radiographs and was acquired using analog techniques, with highly standardized fluoroscopically positioned, semiflexed-view knee radiographs at baseline and 24 months. Patients were defined as progressors using a dichotomous definition of a ≥0.6 mm decrease in JSW from baseline.

Biochemical markers. In both the North American and European groups, an expected dose-dependent decrease in the level of NTX-I with risedronate was observed within 6 months and continued through 24 months, demonstrating effective drug delivery. The mean percent changes from baseline to 24 months for all doses of risedronate were statistically significantly different compared with placebo. In the North American placebo group, a 7.3% increase in the level of NTX-I was seen, with a decrease from baseline of 21.6% in patients receiving risedronate at a dosage of 5 mg/day, a decrease of 29.2% in those receiving risedronate at a dosage of 50 mg/week, and a decrease of 39.2% in the group receiving risedronate at a dosage of 15 mg/day. Similarly, in the European cohort, the level of NTX-I increased by 3.0% in the placebo group, while decreases were seen with all doses of risedronate (29.0% in the group receiving 5 mg/day, 28.2% in those receiving 35 mg/week, and 41.7% in those receiving 15 mg/day).

An early decrease in the level of CTX-II was seen in risedronate-treated patients, although placebo-treated patients had increases over the 24 months of the study. At the highest dosage of risedronate (15 mg/day), reductions of 17.9% and 19.6% from baseline to 24 months were seen in North American patients and European patients, respectively, compared with increases in the North American and European placebo groups of 26.3% and 10.1%, respectively. Even greater reductions in the levels of CTX-II (25–41%) were seen at earlier time points in patients receiving risedronate.

Safety. Risedronate was well tolerated over 2 years, using dosages that were up to 3-fold the currently approved dosage for osteoporosis. No clinically significant differences in any standard laboratory parameters (complete blood cell count, electrolytes, liver function, renal function) were evident in the risedronate-treated groups compared with those receiving placebo (data not shown), and there were no differences in the number of deaths. No significant difference was noted in the number of upper gastrointestinal (GI) adverse events between patients receiving risedronate and those receiving placebo. There were no significant differences between groups for prior GI disease and use of NSAIDs, aspirin, or proton pump inhibitors (data not shown). Upper GI adverse events were defined as abdominal pain, ulcers, esophagitis, gastritis, dyspepsia, dysphagia, hematemesis, and melena. The low rate of GI adverse events is especially notable in patients with OA, of whom >70% had taken an NSAID or aspirin. Furthermore, at the highest risedronate dosage (15 mg/day or a total dose of 105 mg/week), there were fewer adverse events associated with risedronate compared with placebo, although the difference was not statistically significant.

DISCUSSION

The Knee Osteoarthritis Structural Arthritis (KOSTAR) trial was designed to explore the effect of risedronate on JSN and symptoms in patients with mild to moderate knee OA. The risedronate OA research program consisted of 3 studies: a smaller, 285-patient study conducted in the UK (the British Study of Risedronate in Structure and Symptoms of Knee OA [BRISK]), which focused on symptom end points (28), and the 2 phase III studies summarized in this report, which explored changes in JSW and symptoms as primary end points. This is the largest interventional drug development study of knee OA reported to date, with >2,400 patients randomized, and >86.7% completing the month 24 visit. These studies demonstrate the feasibility of using centralized radiography facilities and fluoroscopically aided radiographs for a multinational study.

The previously reported BRISK study showed that risedronate at a dosage of 15 mg/day improved PGA scores over 1 year, with concomitant reductions in the level of a marker of cartilage degradation (CTX-II) (28). Fewer risedronate-treated patients had significant progression over 1 year compared with placebo-treated patients. In the current multinational study, the same techniques of measurement showed that even though risedronate was effective for reducing bone turnover and the level of cartilage degradation markers, no treatment effect was demonstrated for the primary study end points.

Signs and symptoms improved in all groups, including placebo-treated patients, representing a change of ~20% from baseline in symptom end points, including the total WOMAC score, WOMAC subscales, and PGA scores. The magnitude of this improvement has been accepted as clinically relevant at the level of the individual patient as well as in clinical trials (39,40). Furthermore, in patients with lower levels of pain, as seen in this study, previously reported clinically important improvements in both pain and PGA scores were similar to the reductions seen in the KOSTAR trial (40). This improvement was noted at the earliest time point and persisted through the 2 years of the study. There was, however, no demonstrable treatment difference in terms of signs and symptoms for risedronate compared with placebo. In the BRISK study, Spector et al reported an improvement in PGA scores (28); however, the

magnitude of the placebo-associated improvement was not as large as that in the current study, perhaps accounting for the significance of the treatment effect. It is unknown whether the placebo benefit we observed represents expectation bias on the part of patients or whether the WOMAC index is unable to discern a treatment effect at low background pain levels. In a recently completed study of doxycycline (5), patients had a similarly low level of background pain (WOMAC pain scores of 43.2 in the index knee and 36 in the contralateral knee), with no treatment effect on signs and symptoms in spite of an apparent treatment effect on structure in one knee but not the other. The doxycycline study also allowed use of background analgesics, to encourage participant retention over 30 months.

The KOSTAR trial enrolled patients who may have been taking analgesics to control pain at baseline, with >50% of patients in both the European and North American groups taking NSAIDs or coxibs at baseline. The KOSTAR study design was developed in conjunction with regulatory authorities to encourage patient retention over 2 years, recognizing that analgesic requirements are variable and may necessitate switches in medication. Given that traditional flare-design studies of knee OA using active comparators are associated with a withdrawal rate of up to 30% at 6 weeks (41–43) and even more in placebo groups, prohibiting patients from taking rescue medication would have likely resulted in a significant number of withdrawals over time. Other studies of structure-modifying therapies in OA have had dropout rates ranging from 29% to almost 50% over 2–3 years (2,7,44). Using the KOSTAR study design, an impressive 76% of patients completed 2 years without dropping out, and 86.7% completed the 24-month visit.

To account for differences in analgesic regimens, at 5 days preceding study visits, patients were provided with diclofenac and acetaminophen as the only allowable analgesics. These agents were eliminated during the 2 days preceding visits for symptom evaluation. In spite of analgesic washout, patients in the KOSTAR trial had lower levels of baseline pain than have been seen in most other studies of analgesics. Other OA studies in which background analgesic therapy was continued have enrolled only patients with higher levels of background pain, in order to demonstrate a treatment effect (45).

No treatment effect of risedronate was demonstrated for the primary structure end points. The proportions of patients in all treatment groups who demonstrated significant progression (≥0.6 mm of joint space loss) over 2 years were low (including 13% of placebo-treated patients). Most patients showed no change over time or changes were within the measurement error of the technique. In the similarly designed BRISK study, 8% of placebo-treated patients demonstrated progression at 1 year, using an even more stringent definition of progression (0.75 mm of joint space loss). In a study of glucosamine evaluating progression of knee OA using a fixed-extension x-ray and defining significant progression as >0.5 mm of joint space loss, only 14% of placebo-treated patients demonstrated progression over 3 years (2).

The changes in mean JSW in all groups were also smaller than originally anticipated. Although based on results of prior studies (46–50) mean radiographic progression was anticipated to occur at a rate of 0.20 mm per year, in the KOSTAR trial mean radiographic progression was 0.088 mm over 2 years in the European cohort and 0.13 mm in the North American cohort.

Many prior studies evaluating disease modification in OA have shown mean changes that were less than the measurement error of the technique of evaluation. Using the same fluoroscopically positioned flexed-knee view as that used in the KOSTAR trial, Brandt et al (5) found a decrease over 30 months of 0.45 mm in the index knee and 0.41 mm in the contralateral knee in placebo-treated patients; this decrease is more than 3-fold greater than that seen in the KOSTAR study. This may be attributable to enrichment of that study with patients with an identifiable risk factor for disease progression, namely obesity (the mean BMI was 36.7 kg/m^2, compared with 30.3 kg/m^2 in the North American cohort and 29.4 kg/m^2 in the European cohort of the KOSTAR study), or to the fact that patients enrolled in the doxycycline study (5) had more cartilage at baseline. Although the radiographic acquisition method used in the doxycycline study was the same (with the exception of use of digital radiographs), the analysis by Brandt et al used a manual method of determining JSW that, although reproducible, may be less accurate and reliable than the computer-assisted measurements used in the KOSTAR trial (34). In a study of glucosamine using fixed extension radiographs, the mean JSW change over 3 years was 0.19 mm in the placebo group, without enrichment for risks associated with progression (2).

Limb angulation and malalignment have been increasingly recognized as potentially important factors influencing the rates of radiographic progression in OA (51). In our study, however, neither a full-length radiograph nor a clinical assessment of varus and valgus alignment was performed. However, because our study was limited to an assessment of patients in whom medial compartment disease was greater than lateral compart-

ment disease, we would anticipate that malalignment in this population would be predominantly varus in nature. Thus, some of the effects of malalignment introduced in studies that combine medial and lateral compartment disease may have been somewhat mitigated. The ability to assess alignment using fluoroscopically positioned semiflexed-view radiographs, as were obtained in this study, is limited compared with other methods of evaluation (e.g., full-limb films).

Other studies have classified radiographic progression as a worsening of the Kellgren/Lawrence score, which is dependent predominantly on osteophytes, whereas progression in the KOSTAR trial was defined as a significant amount of JSN. Nevertheless, no treatment effect on osteophytes was observed. Although an effect of bisphosphonates on osteophytes has been demonstrated in animal models of OA (19), we did not observe a treatment effect of risedronate. The sensitive radiography technique used to detect changes in JSW may not be ideal for detecting changes in osteophytes over time, because osteophytes may not appear in profile, thus making assessment of their size difficult. It is also more difficult to detect changes in the categorical grading system used for osteophyte size compared with the linear changes derived from JSW measurement.

Many investigators have argued that a "hard" outcome should also be used in studies of SMOADs. Some have suggested that joint replacement represents ultimate joint failure and could be used as such an outcome (52). In this study, only ~3% of patients underwent joint replacement surgeries, some of which may have been planned prior to participation in the study, and there was no difference between treatment groups in the numbers of nontraumatic joint replacements (potentially of nonindex joints). The evaluation of joint failure may be a possible outcome measure in future studies but would likely require much longer periods of followup and even larger numbers of patients.

The retention of patients in the study indicated a high degree of compliance with the regimen. The adverse events recorded did not indicate any differences attributable to risedronate compared with placebo. The numbers of dropouts and withdrawals were similar across groups, and no clear relationship with the dosage of study medication was observed. The tolerability of dosages up to 3-fold the dosage used to treat osteoporosis over 2 years, especially in a population of patients with significant concomitant background use of NSAIDs, was impressive. In spite of concerns about potential GI toxicity with long-term administration of high doses, risedronate was well tolerated, with no increase in the incidence of GI adverse events, as previously observed (53).

Notwithstanding the lack of treatment effects on signs and symptoms or joint space, the demonstration of a dose-dependent reduction in a marker of cartilage degradation (e.g., urinary CTX-II) in response to risedronate was notable in both cohorts. Urinary CTX-II levels are thought to reflect the rate of cartilage degradation, and elevated levels of CTX-II have been seen in patients with imminent progression of OA and correlated with long-term progression (54,55). Similar results were previously reported in the smaller BRISK trial (28). Earlier studies of postmenopausal women and patients with Paget's disease also showed that bisphosphonates reduced the levels of markers of cartilage degradation (56,57). Whether a long-term reduction in the level of CTX-II would translate into a slower rate of progression could not be accurately determined from the current study, due to the limited time period.

The mechanism of action for a reduction in CTX-II levels with risedronate is unclear. This may represent a primary effect on subchondral bone turnover leading to improvement in cartilage stability. Given that in OA subchondral bone the size and number of trabecula are decreased (9), along with the known benefits of bisphosphonates on improving trabecular connectivity and bone strength (58), it is possible that local improvement in subchondral bone strength would better absorb load and translate into decreased levels of biomechanical stressors on cartilage. It is unknown whether a reduction in the level of cartilage degradation markers would correlate with visible joint structure changes using more sensitive imaging, but this remains an important question for future research. Indeed, reductions in the level of CTX-II have been recently reported to track with MR images of subchondral lesions in OA knees over 3 months (59).

This study demonstrates the challenges associated with evaluating a medication that may affect signs and symptoms along with a radiographic outcome and in developing a study design that will evaluate both outcomes. Although controlling pain is important for patient retention in a study, the measures used to control this pain may result in a high placebo response, as demonstrated here. Conversely, although patients with mild pain are potentially appropriate for enrollment in a longer-term study of structure modification, such patients may not be appropriate for studying an effect on signs and symptoms. Plain radiography, even over 2 years, will detect only a small number of progressors, as defined by stringent criteria that take into account the

measurement error of the radiographic technique. As is also the case in RA clinical studies, a small number of patients drive mean changes, with most patients experiencing no change during the course of the study. Defining clinical, biochemical, and genetic predictors of progression is important. Further analyses such as these may indicate a more appropriate group to study for future clinical trials (60,61). Although MRI may be more sensitive in detecting structural changes over time (59,62), additional correlation with plain radiography is still likely to be required by drug regulatory agencies and by the rheumatology community.

ACKNOWLEDGMENTS

We would like to acknowledge participation of the following investigators: in North America, W. Bensen, E. Keystone, H. Tannenbaum (Canada); R. D. Altman, H. S. Baraf, S. B. Herbert, J. M. Bathon, J. A. Block, D. G. Borenstein, A. Brodsky, B. Corser, T. Cupps, J. P. Donohue, R. D. Emkey, J. Fidelholtz, J. Z. Forstot, C. M. Franklin, K. H. Fye, N. Gaylis, J. Geohas, J. S. Gimbel, G. V. Gordon, R. Gordon, T. N. Hangartner, B. K. Harris, R. Katz, S. Kolasinski, J. A. Markenson, M. Neuwelt, C. Radis, W. Riskin, P. Rosenthal, T. Schnitzer, R. Severance, Y. Sherrer, J. Tesser, C. Thorne, N. Wei, M. A. Weitz (US); in Europe, J. Smolen, H. Bröll (Austria); Z. Chicy, K. Pavelka (Czech Republic); P. Bourgeois, A. Kahan, J.-M. LeParc, T. Bardin (France); H. Gaulrapp, V. Jaegermann, H. Rechl, M. Talke, H. Zippel, J. Zacher, A. Wagenitz (Germany); G. Balint (Hungary); B. Bresnihan, E. Casey, C. J. McCarthy, M. G. Molloy, P. O'Connell (Ireland); M. Cutolo, M. Bevilacqua, L. Sinigaglia (Italy); J. W. J. Bijlsma, J. D. Moolenburgh, V. Van de Walle (The Netherlands); E. Czerwinski, A. Filipowicz-Sosnowska, P. Gluszko, R. Lorenc, J. Przedlacki, A. Sawicki, L. Szczepanski, W. Tlustochowicz (Poland); B. Curkovic, A. Pahor, B. Rozman (Slovenia/Croatia).

We thank Curtis Hayes and Cornelius van Kuijk for radiography design and evaluations. We also thank the study coordinators and personnel at all investigative sites and radiography facilities. We gratefully acknowledge the participation of the almost 2,500 patients involved in these clinical trials. We would like to acknowledge the assistance of Ruby Xia and Chad Melson for programming support.

REFERENCES

1. Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum 1998;41:778–99.
2. Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacovelli G, Rovati LC. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. Arch Intern Med 2002;162:2113–23.
3. Biggee BA, Blinn CM, McAlindon TE, Nuite M, Silbert JE. Low levels of human serum glucosamine after ingestion of glucosamine sulphate relative to capability for peripheral effectiveness. Ann Rheum Dis 2006;65:222–6.
4. Clegg DO, Reda DJ, Harris CL, Klein MA, O'Dell JR, Hooper MM, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med 2006; 354:795–808.
5. Brandt KD, Mazzuca SA, Katz BP, Lane KA, Buckwalter KA, Yocum DE, et al. Effects of doxycycline on progression of osteoarthritis: results of a randomized, placebo-controlled, double-blind trial. Arthritis Rheum 2005;52:2015–25.
6. Provvedini DM. The true results of the ECHODIAH study with diacerein [letter]. Osteoporos Int 2003;14:270.
7. Dougados M, Nguyen M, Berdah L, Mazieres B, Vignon E, Lequesne M, for the ECHODIAH Investigators Study Group. Evaluation of the structure-modifying effects of diacerein in hip osteoarthritis: ECHODIAH, a three-year, placebo-controlled trial. Arthritis Rheum 2001;44:2539–47.
8. Messent EA, Buckland-Wright JC, Blake GM. Fractal analysis of trabecular bone in knee osteoarthritis is a more sensitive marker of disease status than bone mineral density. Calcif Tissue Int 2005; 76:419–25.
9. Messent EA, Ward RJ, Tonkin CJ, Buckland-Wright C. Tibial cancellous bone changes in patients with knee osteoarthritis: a short-term longitudinal study using Fractal Signature Analysis. Osteoarthritis Cartilage 2005;13:463–70.
10. Messent EA, Ward RJ, Tonkin CJ, Buckland-Wright C. Cancellous bone differences between knees with early, definite and advanced joint space loss: a comparative quantitative macroradiographic study. Osteoarthritis Cartilage 2005;13:39–47.
11. Karvonen RL, Miller PR, Nelson DA, Granda JL, Fernandez-Madrid F. Periarticular osteoporosis in osteoarthritis of the knee. J Rheumatol 1998;25:2187–94.
12. Conaghan PG, Felson DT. Structural associations of osteoarthritis pain: lessons from magnetic resonance imaging [review]. Novartis Found Symp 2004;260:191–201; discussion 201–5, 277–9.
13. Bergman AG, Willen HK, Lindstrand AL, Pettersson HT. Osteoarthritis of the knee: correlation of subchondral MR signal abnormalities with histopathologic and radiographic features. Skeletal Radiol 1994;23:445–8.
14. Zanetti M, Bruder E, Romero J, Hodler J. Bone marrow edema pattern in osteoarthritic knees: correlation between MR imaging and histologic findings. Radiology 2000;215:835–40.
15. Anderson-MacKenzie JM, Quasnichka HL, Starr RL, Lewis EJ, Billingham ME, Bailey AJ. Fundamental subchondral bone changes in spontaneous knee osteoarthritis. Int J Biochem Cell Biol 2005;37:224–36.
16. Spector TD. Bisphosphonates: potential therapeutic agents for disease modification in osteoarthritis. Aging Clin Exp Res 2003; 15:413–8.
17. Meyer J, Farmer R, Prenger MC. Risedronate but not alendronate slows disease progression in the guinea pig model of primary osteoarthritis [abstract]. J Bone Miner Res 2001;16 Suppl 1:SA472.
18. Meyer JM, Dansereau SM, Farmer RW, Jeans GL, Prenger MC. Bisphosphonates structurally similar to risedronate (actonel) slow disease progression in the guinea pig model of primary osteoarthritis [abstract]. Arthritis Rheum 2001;44 Suppl 9:S307.
19. Hayami T, Pickarski M, Wesolowski GA, Mclane J, Bone A, Destefano J, et al. The role of subchondral bone remodeling in osteoarthritis: reduction of cartilage degeneration and prevention of osteophyte formation by alendronate in the rat anterior cruciate ligament transection model. Arthritis Rheum 2004;50:1193–206.
20. Muehleman C, Green J, Williams JM, Kuettner KE, Thonar EJ, Sumner DR. The effect of bone remodeling inhibition by zoledronic acid in an animal model of cartilage matrix damage. Osteoarthritis Cartilage 2002;10:226–33.
21. Carbone LD, Nevitt MC, Wildy K, Barrow KD, Harris F, Felson

D, et al, for the Health, Aging and Body Composition Study. The relationship of antiresorptive drug use to structural findings and symptoms of knee osteoarthritis. Arthritis Rheum 2004;50: 3516–25.
22. Felson DT, Chaisson CE, Hill CL, Totterman SM, Gale ME, Skinner KM, et al. The association of bone marrow lesions with pain in knee osteoarthritis. Ann Intern Med 2001;134:541–9.
23. Bettica P, Cline G, Hart DJ, Meyer J, Spector TD. Evidence for increased bone resorption in patients with progressive knee osteoarthritis: longitudinal results from the Chingford study. Arthritis Rheum 2002;46:3178–84.
24. Brown JP, Chines AA, Myers WR, Eusebio RA, Ritter-Hrncirik C, Hayes CW. Improvement of pagetic bone lesions with risedronate treatment: a radiologic study. Bone 2000;26:263–7.
25. Burger H, van Daele PL, Odding E, Valkenburg HA, Hofman A, Grobbee DE, et al. Association of radiographically evident osteoarthritis with higher bone mineral density and increased bone loss with age: the Rotterdam Study. Arthritis Rheum 1996;39:81–6.
26. Hosking DJ, Eusebio RA, Chines AA. Paget's disease of bone: reduction of disease activity with oral risedronate. Bone 1998;22: 51–5.
27. Miller PD, Brown JP, Siris ES, Hoseyni MS, Axelrod DW, Bekker PJ, for the Paget's Risedronate/Etidronate Study Group. A randomized, double-blind comparison of risedronate and etidronate in the treatment of Paget's disease of bone. Am J Med 1999;106: 513–20.
28. Spector TD, Conaghan PG, Buckland-Wright JC, Garnero P, Cline GA, Beary JF, et al. Effect of risedronate on joint structure and symptoms of knee osteoarthritis: results of the BRISK randomized, controlled trial [ISRCTN01928173]. Arthritis Res Ther 2005;7:R625–33.
29. Reid DM, Hughes RA, Laan RF, Sacco-Gibson NA, Wenderoth DH, Adami S, et al, for the European Corticosteroid-Induced Osteoporosis Treatment Study. Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial. J Bone Miner Res 2000;15: 1006–13.
30. Harris ST, Watts NB, Li Z, Chines AA, Hanley DA, Brown JP. Two-year efficacy and tolerability of risedronate once a week for the treatment of women with postmenopausal osteoporosis. Curr Med Res Opin 2004;20:757–64.
31. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al, for the Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis Rheum 1986;29:1039–49.
32. Buckland-Wright JC, Bird CF, Ritter-Hrncirik CA, Cline GA, Tonkin C, Hangartner TN, et al. X-ray technologists' reproducibility from automated measurements of the medial tibiofemoral joint space width in knee osteoarthritis for a multicenter, multinational clinical trial. J Rheumatol 2003;30:329–38.
33. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833–40.
34. Buckland-Wright JC, Williams SA, Ward RJ. Accuracy and precision of joint space width measurements in standard and macroradiographs of osteoarthritic knees. Ann Rheum Dis 1995;54: 872–80.
35. Buckland-Wright JC, Wolfe F, Ward RJ, Flowers N, Hayne C. Substantial superiority of semiflexed (MTP) views in knee osteoarthritis: a comparative radiographic study, without fluoroscopy, of standing extended, semiflexed (MTP), and schuss views. J Rheumatol 1999;26:2664–74.
36. Altman RD, Hochberg M, Murphy WA Jr, Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis. Osteoarthritis Cartilage 1995;3 Suppl A:3–70.
37. Christgau S, Garnero P, Fledelius C, Moniz C, Ensig M, Gineyts E, et al. Collagen type II C-telopeptide fragments as an index of cartilage degradation. Bone 2001;29:209–15.
38. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthrosis. Ann Rheum Dis 1957;16:494–501.
39. Angst F, Aeschlimann A, Stucki G. Smallest detectable and minimal clinically important differences of rehabilitation intervention with their implications for required sample sizes using WOMAC and SF-36 quality of life measurement instruments in patients with osteoarthritis of the lower extremities. Arthritis Rheum 2001;45:384–91.
40. Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. Ann Rheum Dis 2005;64:29–-33.
41. Geba GP, Weaver AL, Polis AB, Dixon ME, Schnitzer TJ, for the VACT Group. Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee: a randomized trial. JAMA 2002;287:64–71.
42. Pincus T, Koch G, Lei H, Mangal B, Sokka T, Moskowitz R, et al. Patient Preference for Placebo, Acetaminophen (paracetamol) or Celecoxib Efficacy Studies (PACES): two randomised, double blind, placebo controlled, crossover clinical trials in patients with knee or hip osteoarthritis. Ann Rheum Dis 2004;63:931–9.
43. Pincus T, Koch GG, Sokka T, Lefkowith J, Wolfe F, Jordan JM, et al. A randomized, double-blind, crossover clinical trial of diclofenac plus misoprostol versus acetaminophen in patients with osteoarthritis of the hip or knee. Arthritis Rheum 2001;44:1587–98.
44. Mazzuca SA, Brandt KD, Katz BP, Lane KA, Bradley JD, Heck LW, et al. Subject retention and adherence in a randomized placebo-controlled trial of a disease-modifying osteoarthritis drug. Arthritis Rheum 2004;51:933–40.
45. Emkey R, Rosenthal N, Wu SC, Jordan D, Kamin M. Efficacy and safety of tramadol/acetaminophen tablets (Ultracet) as add-on therapy for osteoarthritis pain in subjects receiving a COX-2 nonsteroidal antiinflammatory drug: a multicenter, randomized, double-blind, placebo-controlled trial. J Rheumatol 2004;31: 150–6.
46. Lequesne M. Quantitative measurements of joint space during progression of osteoarthritis: "chondrometry." In: Kuettner K, Goldberg V, editors. Osteoarthritic disorders. Rosemont (IL): American Academy of Orthopaedic Surgeons; 1995. p. 427–44.
47. Ravaud P, Giraudeau B, Auleley GR, Edouard-Noel R, Dougados M, Chastang C. Assessing smallest detectable change over time in continuous structural outcome measures: application to radiological change in knee osteoarthritis. J Clin Epidemiol 1999;52: 1225–30.
48. Buckland-Wright JC, Macfarlane DG, Jasani MK, Lynch JA. Quantitative microfocal radiographic assessment of osteoarthritis of the knee from weight bearing tunnel and semiflexed standing views. J Rheumatol 1994;21:1734–41.
49. Kirwan JR, Cushnaghan J, Dacre J, McAlindon T, Dieppe PA, Rogers J. Progression of joint space narrowing in knee osteoarthritis [abstract]. Arthritis Rheum 1992;35 Suppl 9:S134.
50. Buckland-Wright JC, Macfarlane DG, Lynch JA, Jasani MK. Quantitative microfocal radiography detects changes in OA knee joint space width in patients in placebo controlled trial of NSAID therapy. J Rheumatol 1995;22:937–43.
51. Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. JAMA 2001;286:188–95.
52. Dougados M, Gueguen A, Nguyen M, Berdah L, Lequesne M, Mazieres B, et al. Requirement for total hip arthroplasty: an outcome measure of hip osteoarthritis? J Rheumatol 1999;26: 855–61.

53. Adami S, Pavelka K, Cline GA, Hosterman MA, Barton IP, Cohen SB, et al. Upper gastrointestinal tract safety of daily oral risedronate in patients taking NSAIDs: a randomized, double-blind, placebo-controlled trial. Mayo Clin Proc 2005;80:1278–85.
54. Garnero P, Landewe R, Boers M, Verhoeven A, van der Linden S, Christgau S, et al. Association of baseline levels of markers of bone and cartilage degradation with long-term progression of joint damage in patients with early rheumatoid arthritis: the COBRA study. Arthritis Rheum 2002;46:2847–56.
55. Reijman M, Hazes JM, Bierma-Zeinstra SM, Koes BW, Christgau S, Christiansen C, et al. A new marker for osteoarthritis: cross-sectional and longitudinal approach. Arthritis Rheum 2004;50: 2471–8.
56. Lehmann HJ, Mouritzen U, Christgau S, Cloos PA, Christiansen C. Effect of bisphosphonates on cartilage turnover assessed with a newly developed assay for collagen type II degradation products. Ann Rheum Dis 2002;61:530–3.
57. Garnero P, Christgau S, Delmas PD. The bisphosphonate zoledronate decreases type II collagen breakdown in patients with Paget's disease of bone. Bone 2001;28:461–4.
58. Borah B, Dufresne TE, Chmielewski PA, Johnson TD, Chines A, Manhart MD. Risedronate preserves bone architecture in postmenopausal women with osteoporosis as measured by three-dimensional microcomputed tomography. Bone 2004;34:736–46.
59. Garnero P, Peterfy C, Zaim S, Schoenharting M. Bone marrow abnormalities on magnetic resonance imaging are associated with type II collagen degradation in knee osteoarthritis: a three-month longitudinal study. Arthritis Rheum 2005;52:2822–9.
60. Bingham CO III, Cline G, Adami S, Buckland-Wright C, Cohen S, Conaghan P, et al. Predictors of structural progression in knee osteoarthritis over 24 months [abstract]. Osteoarthritis Cartilage 2004;12 Suppl B:S136.
61. Lohmander LS, Felson D. Can we identify a 'high risk' patient profile to determine who will experience rapid progression of osteoarthritis? Osteoarthritis Cartilage 2004;12 Suppl A: S49–52.
62. Raynauld JP, Martel-Pelletier J, Berthiaume MJ, Labonte F, Beaudoin G, de Guise JA, et al. Quantitative magnetic resonance imaging evaluation of knee osteoarthritis progression over two years and correlation with clinical symptoms and radiologic changes. Arthritis Rheum 2004;50:476–87.

How do we know that the pain in fibromyalgia is “real”?

Richard E. Harris Ph.D.

Daniel J. Clauw M.D.

Department of Medicine, Division of Rheumatology

University of Michigan Medical Center

24 Frank Lloyd Wright Dr. PO Box 385

Ann Arbor MI 18106

Abstract. Fibromyalgia is a common idiopathic pain condition often resulting in increased morbidity and disability in patients. The lack of peripheral abnormalities in this disease has lead clinicians and researchers alike to question if this syndrome represents a valid entity. Recent genetic findings suggest that specific gene mutations may predispose individuals to develop fibromyalgia. In addition neurobiological studies indicate that fibromyalgia patients have abnormalities within central brain structures that normally encode pain sensations in healthy pain free controls. Future studies that focus on central neurobiological and/or genetic influences in fibromyalgia may bring insight into mechanisms of this problematic disease and ultimately result in improved treatments.

Introduction. Fibromyalgia is a common systemic disorder estimated to affect 2% to 4% of the population, second in prevalence among rheumatologic conditions to osteoarthritis [1]. There are legitimate controversies surrounding many aspects of fibromyalgia, including precisely how it should be defined, as well as whether individuals with this condition are disabled or deserve compensation. [2]. At the same time, however, there have been rapid advances in our aggregate scientific knowledge about fibromyalgia. There are now multiple, converging lines of evidence confirming that the pain of fibromyalgia is "real", and that there are strong neurobiological underpinnings to this condition. [3]. In fact, there has been a parallel recognition that many pain syndromes classically thought to be "idiopathic," such as irritable bowel syndrome, tension headache, temporomandibular syndrome, and idiopathic low back pain, share overlapping symptom expression and underlying mechanisms with fibromyalgia [4-6].

The American College of Rheumatology criteria for fibromyalgia: the good and the bad. In 1990, the American College of Rheumatology established classification criteria for fibromyalgia [7] These criteria require that an individual must have *both* chronic widespread pain involving all four quadrants of the body as well as the axial skeleton, *and* the presence of 11 of 18 tender points on examination. Two positive aspects of the ACR criteria are that: 1) as intended, these allowed investigators throughout the world to use a single set of classification criteria to standardize research studies, and 2) these criteria require that individuals display

widespread tenderness in addition to pain. In fact, many of the mechanistic and physiological studies of fibromyalgia have explored the underlying mechanism(s) for this tenderness (see below). However, the ACR criteria have not been as uniformly positive in the societal sense. Two of the (unintended) consequences of these criteria are that they: 1) are often used in clinical practice to diagnose individual patients in clinical settings (this was not the intended purpose and should not be rigidly adhered to) and 2) skew the diagnosis of fibromyalgia towards primarily being women with high levels of distress (by assessing tenderness by "counting tender points").

The problems with tender points. When the ACR criteria were published, it was thought that tender points were somehow areas that were increasingly tender in individuals with fibromyalgia, and many therapies were even specifically at reducing tender points (e.g., injections with anesthetics or corticosteroids). Since then, research has definitively shown that patients with fibromyalgia have tenderness or decreased pain thresholds extending throughout their body, and not only at localized areas considered tender points [8;9]. Thus, we now know that tender point are merely areas where anyone is more tender, and that overall tenderness in an individual can be successfully predicted by just assessing this in a few regions of the body. Furthermore, although women are only 1.5 times more likely than men to experience chronic widespread pain, they are 10 times more likely than men to have more than 11 tender points on examination, and thus the overwhelming majority of males with chronic widespread pain will not meet criteria for fibromyalgia (even though they likely have the same condition) [10]. Additionally, Wolfe was the first to show that in population-based studies, the number of tender points an individual has is highly correlated with how "distressed" they are [11]. This led many to believe that tenderness and distress were inexplicably linked. However, more sophisticated measures of pressure pain threshold that give individuals stimuli in a random, unpredictable fashion, show: 1) that these measures of tenderness are not influenced by an individuals' current psychological distress, and 2) that individuals with fibromyalgia are still found to be much more tender than healthy controls using these more sophisticated measures. Thus, requiring that individuals have a certain number of tender points in order to fulfill criteria for fibromyalgia skews the diagnosis from those who have chronic widespread pain alone (a

group that would be comprised of 1/3 males and only mildly overall elevated levels of distress) to a group that is almost exclusively female and has high levels of distress. Unfortunately, this has likely helped reinforce the notion to some that fibromyalgia is a "psychological condition" affecting primarily females.

What does tenderness really mean? A common finding in fibromyalgia and other "central" pain syndromes is increased tenderness to pressure, which can be classified as mechanical hyperalgesia (i.e., increased pain in response to normally painful stimuli) and/or mechanical allodynia (i.e., pain in response to normally non-painful stimuli) [9;12]. In addition to these findings, fibromyalgia patients and those with related syndromes will often display a decreased noxious threshold to many different types of sensory stimuli, including heat, electrical, and sound. Although skeptics sometimes question the veracity of these findings because they rely on patient self-report of pain and thus could be due to psychological factors, more sophisticated pain testing paradigms have suggested that these findings are not likely to be due to psychological factors. There are a number of other conditions where similar findings have been noted, including irritable bowel syndrome, temporomandibular syndrome, tension headache, idiopathic low back pain, and vulvodynia [13-22]. This has led most investigators to conclude that these conditions share some common pathophysiological mechanisms involving augmented pain or sensory processing in the central nervous system.

Until very recently, there were no studies that examined whether the hyperalgesia "caused" the pain in these "central pain syndromes", or occurred because of the pain. In arguably the best such study performed to date, Diathchenko, Maixner, and colleagues performed a longitudinal study of 202 young pain free women, and followed them for two years, with the outcome of interest being those women who developed new onset of temporomandibular disorder (TMD) [insert bullet 23]. 15 individuals developed TMD over the course of this study, and an individual's central pain threshold at baseline (i.e. while asymptomatic, at the beginning of the study) was a strong predictor of the development of TMD. Moreover, these investigators showed that polymorphisms in the catecholamine-O-methyltransferase (COMT) enzyme predicted both the individual's baseline pain sensitivity, as well as the risk of developing TMD. These data are consistent with Zubieta et. al., who had shown that COMT polymorphisms predicted pain threshold (as measured both by experimental pain

testing and functional neuroimaging) in healthy normal individuals [24]. Fibromyalgia and related conditions have a very strong genetic predisposition, and many of the polymorphisms responsible for having an increased risk of developing these conditions likely affect sensory processing [25; insert bullet 26]. In aggregate, these studies, as well as a plethora of animal data, suggest that pain sensitivity is at least partially genetically determined, and has both "trait" (i.e. it relatively stable over time) and "state" (it can be influenced by external factors and improved with treatment) characteristics [27].

Functional imaging results that corroborate the finding that the decreased pain threshold in these conditions is real. Until recently, the finding of augmented stimulation-evoked pain noted above was entirely reliant on patient self-report. Functional neuroimaging can give a more objective assessment of how an individual responds to pain, by measuring the magnitude of neuronal activation that occurs in brain regions when individuals are given similar objective stimuli. These methods infer increased neural activity from highly localized increases in regional cerebral blood flow produced in response to anticipated metabolic demands. These methods can use infusion of radioactive tracers (e.g. PET or SPECT), or in the case of functional MRI (fMRI), use the magnetic properties of oxygenated hemoglobin in the blood as an indirect, intrinsic tracer.

Single-Photon-Emission Computed Tomographic (SPECT) was the first functional neuroimaging technique to be used in fibromyalgia. SPECT imaging involves the introduction of radioactive compounds into the participant's blood stream, which then decay over time giving a window for neural activity assessment. The first trial using SPECT imaging in FM patients was conducted by Mountz et al [insert bullet 28]. Their data from 10 FM patients and 7 age- and education-matched healthy controls indicated that both the caudate and the thalamus of FM patients had decreased blood flow. The findings by Mountz et al. were largely replicated in a second SPECT study by Kwiatek et al. [29]. In a third SPECT trial, Guedj et al. reported a study using a more sensitive radioligand (99mTc-ECD) in FM patients and pain free controls [30]. Guedj et al. found hyperperfusion in FM patients within the somatosensory cortex and hypoperfusion in the anterior and posterior cingulate, the amygdala, medial frontal and parahippocampal gyrus, and the cerebellum. Finally, if these rCBF differences are relevant for fibromyalgia pathology, one could hypothesize that changes in rCBF should track

with changes in pain symptoms over time. One longitudinal treatment trial used SPECT imaging to assess changes in rCBF following administration of amitriptyline within 14 FM patients [31]. After three months of treatment with amitriptyline, increases in rCBF in the bilateral thalamus and the basal ganglia were observed. Since the same two regions had been implicated previously, these data suggest that amitriptyline may normalize the altered blood flow thereby reducing pain symptoms.

Functional MRI (fMRI). fMRI is a non-invasive brain imaging technique that relies on changes in the relative concentration of oxygenated to deoxygenated hemoglobin within the brain. In response to neural activity, oxygenated blood flow is increased within the local brain area. This causes a decrease in the concentration of deoxygenated hemoglobin. Since deoxygenated hemoglobin is paramagnetic, this in turn causes a change in the magnetic property of the tissue. Unlike SPECT and PET which can measure baseline levels of blood flow, the fMRI BOLD signal originates from a difference between experimental conditions and does not assess baseline blood flow. Typically in fibromyalgia trials involving fMRI, evoked pain sensations are compared to "off" conditions that have either no pain or involve an innocuous sensation.

The first trial to use fMRI in fibromyalgia patients was done by Gracely et al. In this study 16 fibromyalgia patients and 16 matched controls were exposed to painful pressures during the fMRI experiment [insert bullet 32]. The authors found increased neural activations (i.e. increases in the BOLD signal) in patients compared to pain free controls, when stimuli of equal pressure magnitude were administered. Regions of increased activity included the primary and secondary somatosensory cortex, the insula, and the anterior cingulate, all regions commonly observed in fMRI studies of healthy normal subjects during painful stimuli. Interestingly, when the pain free controls were subjected to pressures that evoked equivalent pain ratings in the fibromyalgia patients, similar activation patterns were observed. These findings were entirely consistent with the "left-shift" in stimulus-response function noted with experimental pain testing, and suggest that fibromyalgia patients experience an increased gain or "volume setting" in brain sensory processing systems. In a similar experiment, Cook et al. used painful heat stimuli during fMRI of 9 fibromyalgia patients and 9 pain free controls [33]. Similar to the Gracely et al. findings, the authors observed significant increases in the pain

ratings of patients and augmented pain processing within the contralateral insula. fMRI has also proved useful in determining how co-morbid psychological factors influence pain processing in fibromyalgia. For example, a recent study by Giesecke et al. explored the relationship between depression and enhanced evoked pain sensations in 30 patients with fibromyalgia [34]. The authors found that the anterior insula and amygdala activations were correlated with depressive symptoms, consistent with these regions being involved with affective or motivational aspects of pain processing. However, the degree of neuronal activation in areas of the brain thought to be associated with the "sensory" processing of pain (i.e. where the pain is localized and how intense it is) were not associated with levels of depressive symptoms, or the presence or absence of major depression. These data are consistent with a plethora of evidence in the pain field that there are different regions of the brain responsible for pain processing devoted to sensory intensity versus affective aspects of pain sensation, and suggest that the former and latter are largely independent of each other. In contrast, this same group showed that the presence of catastrophizing, a patient's negative or pessimistic appraisal of their pain, influences both the sensory and affective dimensions of pain on fMRI in fibromyalgia [35].

What does this all mean? Within the population, there are large inter-individual differences in the function of most physiological parameters, leading to fairly large differences in the population in parameters such as blood pressure, blood glucose, etc. Typically, being at either end of the "bell-shaped curve" of the distribution of these functions is associated with illness, such as occurs with low or high blood sugar or pressure. Similarly, body systems such as the immune system have widely varying levels of function, and either hypo- or hyper-activity is associated with disease. This analogy can be carried to these illnesses, because we have learned that these conditions essentially represent a hyperactivity of pain processing mechanisms. This may involve just a region of the body or the entire body. There are many candidate inhibitory and facilitatory influences on pain processing that can act either regionally (at the level of the peripheral nerve or spinal cord) or systemically (at the level of the spinal cord or brain) to cause this "increased gain" in pain processing. In fibromyalgia in particular, there is evidence for both a defect in the function of descending inhibitory

[analgesic] pathways), and/or a concurrent or independent increase in spinal excitatory activity as occurs in wind-up or central sensitization [36;37].

Biochemical studies performed on biological samples from fibromyalgia patients have supported the notion that the pathology might be due to high levels of pronociceptive compounds, low levels of antinociceptive compounds, or both. For example, four studies have identified much higher levels of the pronociceptive substance P in the cerebrospinal fluid (CSF) of patients with fibromyalgia versus control subjects [38]. Elevated substance P is not specific for fibromyalgia because it occurs in other chronic pain states, such as chronic daily headaches and chronic neck or shoulder pain associated with whiplash injury [39;40]. Thus, high CSF substance P appears to be a biological marker for increased pronociceptive activity and a state of increased gain in sensory processing systems.

Conversely, there is considerable evidence that this increased gain could occur because of a deficiency in the one of the major endogenous analgesic pathways, the descending antinociceptive serotonergic–noradrenergic pathway. Studies have shown that the principal metabolite of norepinephrine, 3-methoxy-4-hydroxyphenethylene, is lowered in the CSF of fibromyalgia patients [41]. Similarly, there are data suggesting low serotonin in this syndrome, as manifested by both reduced levels of serotonin and its precursor, L-tryphtophan, in the blood serum of patients with fibromyalgia, as well as reduced levels of the principal serotonin metabolite, 5-hydroxyindole acetic acid, in the CSF [41;42].

The ultimate proof that these defective central control mechanisms are playing a role in fibromyalgia and other central pain states comes from randomized clinical trials demonstrating that neuroactive compounds that either increase inhibitory, such as serotonin-norepinephrine reuptake inhibitors or decrease facilitatory activity, such as anti-epileptics, can be efficacious in the treatment of fibromyalgia as well as neuropathic pain [43;44].

Conclusion. There are now overwhelming data suggesting that fibromyalgia and a number of overlapping pain syndromes are characterized in part by augmented central nervous system processing of pain, as evidenced by hyperalgesia and/or allodynia on examination. This phenomenon can occur in association with

certain psychological factors (e.g. catastrophizing), but psychological factors are not in any way required for an individual to develop or maintain this augmented central pain state. Similar pharmacological (e.g., tricyclics, dual re-uptake inhibitors, anticonvulsants) and non-pharmacological therapies (e.g. aerobic exercise) that are known to act to increase anti-nociceptive or decrease pro-nociceptive influences are efficacious in treating all of these overlapping conditions.

Although there are many legitimate areas of debate and gaps in knowledge regarding these conditions, this is true of any area of scientific inquiry. It is time for us to move past the rhetoric about whether these conditions are real, and take these patients seriously as we endeavor to learn more about the causes and most effective treatments for these disorders.

Reference List

1. Wolfe,F: 50 years of antirheumatic therapy: the prognosis of rheumatoid arthritis. *J Rheumatol Suppl* 22:24-32, 1990

2. Hadler,NM: "Fibromyalgia" and the medicalization of misery. *J Rheumatol* 30:1668-1670, 2003

3. Crofford,LJ, Clauw,DJ: Fibromyalgia: where are we a decade after the American College of Rheumatology classification criteria were developed? *Arthritis Rheum* 46:1136-1138, 2002

4. Bendtsen,L: Central sensitization in tension-type headache--possible pathophysiological mechanisms [In Process Citation]. *Cephalalgia* 20:486-508, 2000

5. Chang,PF, Arendt-Nielsen,L, Graven-Nielsen,T, Chen,AC: Psychophysical and EEG responses to repeated experimental muscle pain in humans: pain intensity encodes EEG activity. *Brain Res Bull* 59:533-543, 2003

6. Bragdon,EE, Light,KC, Costello,NL, Sigurdsson,A, Bunting,S, Bhalang,K, Maixner,W: Group differences in pain modulation: pain-free women compared to pain-free men and to women with TMD. *Pain* 96:227-237, 2002

7. Wolfe,F, Smythe,HA, Yunus,MB, Bennett,RM, Bombardier,C, Goldenberg,DL, Tugwell,P, Campbell,SM, Abeles,M, Clark,P: The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis & Rheumatism* 33:160-172, 1990

8. Petzke,F, Khine,A, Williams,D, Groner,K, Clauw,DJ, Gracely,RH: Dolorimetry performed at 3 paired tender points highly predicts overall tenderness. *Journal of Rheumatology* 28:2568-2569, 2001

9. Granges,G, Littlejohn,G: Pressure pain threshold in pain-free subjects, in patients with chronic regional pain syndromes, and in patients with fibromyalgia syndrome. *Arthritis & Rheumatism* 36:642-646, 1993

10. Wolfe,F, Ross,K, Anderson,J, Russell,IJ: Aspects of fibromyalgia in the general population: Sex, pain threshold, and fibromyalgia symptoms. *Journal of Rheumatology* 22:151-156, 1995

11. Petzke,F, Gracely,RH, Khine,A, Clauw,DJ: Pain sensitivity in patients with fibromyalgia (FM): Expectancy effects on pain measurements. *Arthritis & Rheumatism* 42:S342, 1999

12. Mense,S, Hoheisel,U, Reinert,A: The possible role of substance P in eliciting and modulating deep somatic pain. *Progress in Brain Research* 110:125-135, 1996

13. Teders,SJ, Blanchard,EB, Andrasik,F, Jurish,S, Neff,DF, Arena,J: Relaxation training for tension headache: Comparative efficacy and cost-effectiveness of a minimal therapist contact versus a therapist-delivered procedure. *Behavior Therapy* 15:59-70, 1984

14. Wilder-Smith,OH, Tassonyi,E, Arendt-Nielsen,L: Preoperative back pain is associated with diverse manifestations of central neuroplasticity. *Pain* 97:189-194, 2002

15. Kashima,K, Rahman,OI, Sakoda,S, Shiba,R: Increased pain sensitivity of the upper extremities of TMD patients with myalgia to experimentally-evoked noxious stimulation: Possibility of worsened endogenous opioid systems. *Cranio* 17:241-246, 1999

16. Maixner,W, Fillingim,R, Booker,D, Sigurdsson,A: Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain. *Pain* 63:341-351, 1995

17. Leffler,AS, Hansson,P, Kosek,E: Somatosensory perception in a remote pain-free area and function of diffuse noxious inhibitory controls (DNIC) in patients suffering from long-term trapezius myalgia. *Eur J Pain* 6:149-159, 2002

18. Whitehead,WE, Holtkotter,B, Enck,P, Hoelzl,R, Holmes,KD, Anthony,J, Shabsin,HS, Schuster,MM: Tolerance for rectosigmoid distention in irritable bowel syndrome. *Gastroenterology* 98:1187-1192, 1990

19. Gibson,SJ, Littlejohn,GO, Gorman,MM, Helme,RD, Granges,G: Altered heat pain thresholds and cerebral event-related potentials following painful CO2 laser stimulation in subjects with fibromyalgia syndrome. *Pain* 58:185-193, 1994

20. Kosek,E, Ekholm,J, Hansson,P: Increased pressure pain sensibility in fibromyalgia patients is located deep to the skin but not restricted to muscle tissue [published erratum appears in Pain 1996 Mar;64(3):605]. *Pain* 63:335-339, 1995

21. Giesecke,J, Reed,BD, Haefner,HK, Giesecke,T, Clauw,DJ, Gracely,RH: Quantitative Sensory Testing in Vulvodynia Patients and Increased Peripheral Pressure Pain Sensitivity. *Obstet Gynecol* 104:126-133, 2004

22. Giesecke,T, Gracely,RH, Grant,MA, Nachemson,A, Petzke,F, Williams,DA, Clauw,DJ: Evidence of augmented central pain processing in idiopathic chronic low back pain. *Arthritis Rheum* 50:613-623, 2004

23. Diatchenko,L, Slade,GD, Nackley,AG, Bhalang,K, Sigurdsson,A, Belfer,I, Goldman,D, Xu,K, Shabalina,SA, Shagin,D, Max,MB, Makarov,SS, Maixner,W: Genetic basis for individual variations in pain perception and the development of a chronic pain condition. *Hum Mol Genet* 14:135-143, 2005

This is the first report of a genetic polymorphism that predicts the development of a chronic pain condition. Similar findings may result in studies of fibromylagia.

24. Zubieta,JK, Heitzeg,MM, Smith,YR, Bueller,JA, Xu,K, Xu,Y, Koeppe,RA, Stohler,CS, Goldman,D: COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. *Science* 299:1240-1243, 2003

25. Buskila,D, Neumann,L: Genetics of fibromyalgia. *Curr Pain Headache Rep* 9:313-315, 2005

26. Arnold,LM, Hudson,JI, Hess,EV, Ware,AE, Fritz,DA, Auchenbach,MB, Starck,LO, Keck,PE, Jr.: Family study of fibromyalgia. *Arthritis Rheum* 50:944-952, 2004

This article suggests that fibromyalgia has a strong genetic component.

27. Mogil, J. S. and McCarson, K. E. Finding pain genes: bottom-up and top-down approaches. Journal of Pain . 2004.

Ref Type: In Press

28. Mountz,JM, Bradley,LA, Modell,JG, Alexander,RW, Triana-Alexander,M, Aaron,LA, Stewart,KE, Alarcon,GS, Mountz,JD: Fibromyalgia in women. Abnormalities of regional cerebral blood flow in the thalamus and the caudate nucleus are associated with low pain threshold levels. *Arthritis Rheum* 38:926-938, 1995

This article was the first description of functional neuronal brain differences between fibromyalgia patients and pain free controls.

29. Kwiatek,R, Barnden,L, Tedman,R, Jarrett,R, Chew,J, Rowe,C, Pile,K: Regional cerebral blood flow in fibromyalgia: single-photon-emission computed tomography evidence of reduction in the pontine tegmentum and thalami. *Arthritis Rheum* 43:2823-2833, 2000

30. Guedj,E, Taieb,D, Cammilleri,S, Lussato,D, de Laforte,C, Niboyet,J, Mundler,O: (99m)Tc-ECD brain perfusion SPECT in hyperalgesic fibromyalgia. *Eur J Nucl Med Mol Imaging* 2006

31. Adiguzel,O, Kaptanoglu,E, Turgut,B, Nacitarhan,V: The possible effect of clinical recovery on regional cerebral blood flow deficits in fibromyalgia: a prospective study with semiquantitative SPECT. *South Med J* 97:651-655, 2004

32. Gracely,RH, Petzke,F, Wolf,JM, Clauw,DJ: Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis Rheum* 46:1333-1343, 2002

This article was the first study to show that fibromyalgia patients have enhanced neural activity in pain encoding regions of the brain.

33. Cook,DB, Lange,G, Ciccone,DS, Liu,WC, Steffener,J, Natelson,BH: Functional imaging of pain in patients with primary fibromyalgia. *J Rheumatol* 31:364-378, 2004

34. Giesecke,T, Gracely R H, Williams,DA, Geisser,M, Petzke,F, Clauw,DJ: The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort. *Arthritis & Rheumatism* 52:1577-1584, 2005

35. Gracely,RH, Geisser,ME, Giesecke,T, Grant,MA, Petzke,F, Williams,DA, Clauw,DJ: Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain* 127:835-843, 2004

36. Julien,N, Goffaux,P, Arsenault,P, Marchand,S: Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. *Pain* 114:295-302, 2005

37. Staud,R, Vierck,CJ, Cannon,RL, Mauderli,AP, Price,DD: Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. *Pain* 91:165-175, 2001

38. Russell,IJ, Orr,MD, Littman,B, Vipraio,GA, Alboukrek,D, Michalek,JE, Lopez,Y, MacKillip,F: Elevated cerebrospinal fluid levels of substance P in patients with the fibromyalgia syndrome. *Arthritis & Rheumatism* 37:1593-1601, 1994

39. Sarchielli,P, Alberti,A, Floridi,A, Gallai,V: Levels of nerve growth factor in cerebrospinal fluid of chronic daily headache patients. *Neurology* 57:132-134, 2001

40. Alpar,EK, Onuoha,G, Killampalli,VV, Waters,R: Management of chronic pain in whiplash injury. *J Bone Joint Surg Br* 84:807-811, 2002

41. Russell,IJ, Vaeroy,H, Javors,M, Nyberg,F: Cerebrospinal fluid biogenic amine metabolites in fibromyalgia/fibrositis syndrome and rheumatoid arthritis. *Arthritis & Rheumatism* 35:550-556, 1992

42. Yunus,MB, Dailey,JW, Aldag,JC, Masi,AT, Jobe,PC: Plasma tryptophan and other amino acids in primary fibromyalgia: A controlled study. *Journal of Rheumatology* 19:90-94, 1992

43. Arnold,LM, Keck,PEJ, Welge,JA: Antidepressant treatment of fibromyalgia. A meta-analysis and review. *Psychosomatics* 41:104-113, 2000

44. Goldenberg,DL, Burckhardt,C, Crofford,L: Management of fibromyalgia syndrome. *JAMA* 292:2388-2395, 2004

The Journal of Pain, Vol 7, No 11 (November), 2006: pp 797-799
Available online at www.sciencedirect.com

ELSEVIER

COMMENTARY

The Allure of a Cure

Michael E. Geisser,*,† Randy S. Roth,* and David A. Williams,†,‡

*The Spine Program, Department of Physical Medicine and Rehabilitation;
†Chronic Pain and Fatigue Research Center; and
‡Department of Internal Medicine, Division of Rheumatology; University of Michigan Health System, Ann Arbor, Michigan.

Gatchel and Okifuji's report on the cost-effectiveness of comprehensive pain programs (CPPs) for chronic nonmalignant pain (CNP) does an excellent job of demonstrating the superior ability of CPPs to address the myriad of problems associated with chronic pain. They trace the development of CPPs to the emergence of the biopsychosocial model acknowledging the complex etiology of CNP that involves interplay between biological, psychological, and social factors. Despite the documented success of CPPs, the authors indicate that these programs are significantly underutilized in the treatment of CNP. The most common reason given for their underutilization is the perception of high cost by many third-party payers. Rational arguments refuting the claim of high costs, however, are nicely summarized by Gatchel and Okifuji as well as by Turk et al.[13] So, if not high costs, why are these programs underutilized? We explore alternative explanations to this question.

An Accurate but Unwanted Message

A desire for pain relief is deeply rooted in our make-up. Acute pain warns of actual or potential damage, and, as such, promotes self-preservation. To ignore, cope with, or calmly accept pain while continuing to enjoy daily activities should seem maladaptive and at odds with a basic drive for survival. Thus, it is understandable why patients view elimination of pain as the primary objective of care. CPPs (based on the biopsychosocial model) do not promise cures and as such are less desirable "treatment" options to patients and some providers as well.

CPPs cannot offer cures because, as Gatchel and Okifuji point out, more than 25 years of research on chronic pain has raised serious doubts about the sufficiency of simply altering physiological pain pathways as a means of eliminating most forms of chronic pain. However, despite insufficient empirically driven outcomes and unfavorable costs compared with CPPs, interventions such as injections, surgeries, ablations, and electrical stimulation of pain pathways continue to proliferate. Acceptance of CPPs is not likely to improve so long as hopes for cures for CNP continue to be widely offered and embraced (regardless of how well supported). We should note that the hope for improvement in pain is not inconsistent with the viewpoint espoused by the biopsychosocial model.

Patient Burden

Another unsavory message associated with CPPs is that outcomes depend on the involvement of the patient. For the patient, the experience of chronic pain is shattering to one's confidence in his or her body and to one's perceived ability to participate meaningfully in life. At a time of perceived personal failings, vulnerability, and self-doubt, patients often want to secede from responsibility and surrender control to someone else who might have more expertise on how to make their lives better. CPPs, on the other hand, place much of the responsibility for positive outcomes on the participation of the patient. The juxtaposition between biomedical interventions and CPPs regarding the role of the patient, again, underscores how CPPs could be considered a second choice by patients despite the overwhelming empirical support for its effectiveness. Hope loses its magic when the onus for success is back in the hands of the person with the problem.

Lack of Standardization

For third-party payers, CPPs present problems in quantification. Unlike a drug that is the same regardless of

Address reprint requests to Michael E. Geisser, PhD, University of Michigan Health System, The Spine Program, 325 East Eisenhower Parkway, Ann Arbor, MI 48108. E-mail: mgeisser@umich.edu
1526-5900/$32.00

doi:10.1016/j.jpain.2006.09.007

who takes it, outcomes from multidisciplinary interventions can vary along many parameters, including; (a) content, (b) therapist skill, and (c) patient involvement. It is often difficult to find qualified multidisciplinary providers and, when CPPs are located at limited tertiary care or urban settings, it is difficult to recommend to patients that they travel regularly over great distances to participate in such programs. Third-party payers also want high patient satisfaction in shorter time frames than are reasonably supported by current understandings of pain mechanisms. While CPPs demonstrate good outcomes in numerous domains including quality of life,[5] it remains a risky proposition to promote a potentially unpopular intervention where success depends on active participation over long periods of time.

The Need for Better Education in Pain

CPPs are bitter medicine, and, as such, the value of CPPs is not likely to be embraced until patients and clinicians abandon antiquated and simple notions about what constitutes a positive outcome for chronic pain. Patients with chronic pain often present with a constellation of pain, decreased physical functioning, depressed mood, and poor quality of life. Dissatisfaction with treatment and health care seeking is not likely to stop with a reduction in perceived pain. For example, research among persons with CNP has consistently found that there is little or no relation between clinical pain intensity and disability among persons with chronic pain.[6,10,16] We recently completed a clinical trial for chronic low back pain[7] in which subjects reported no change in perceived function despite statistically significant reductions in pain. Related to these points, Turk et al[14] reported that pain intensity failed to have a direct impact on depressed mood among persons with chronic pain. For chronic spine or back pain, there is strong evidence to support radiographic findings being poorly associated with pain severity and being even less related to pain disability.[1,3,8,17] Newer models of pain focus not only on peripheral factors but heavily on central mechanisms (including psychological factors), as each appears to play critical roles in understanding and treating CNP.[4,11]

The Need to Better Match Patients to Treatments

While beyond the scope of Gathel and Okifuji's review, we believe that there are ways in which CPPs could be made even more cost-effective through careful evaluation of persons with CNP. Because individuals with CNP are a heterogeneous population, recent research suggests that those who have more complex and severe pain problems appear to benefit most from the intensive and specialized intervention offered in CPPs.[9,15] Comprehensive evaluation of the patient with CNP may be highly useful in matching patients with the most efficacious and cost-effective treatments.

In addition, there is an abundance of literature suggesting that response to many interventions for CNP, such as surgery and injections, is accurately predicted by psychosocial factors.[2,12] In practice, it is surprising how little pre-screening this is utilized.

Enhancing Access to CPPs

One difficulty in enhancing the availability of CPPs is the need to assemble a multidisciplinary team. It is sometimes difficult to find allied health professionals who have expertise in dealing with chronic pain, and it is hard to justify hiring a psychologist or other allied health personnel in a private practice setting where the practice may not have sufficient patient volume to justify the expense of the allied health professional. Because of this, it is generally easier to assemble a multidisciplinary team within a tertiary care setting as the personnel needed to assemble a multidisciplinary team are generally available.

The availability of the Internet and telehealth capabilities is also making it possible to offer behavioral aspects of multidisciplinary services to populations that do not have ready access to multidisciplinary clinics. One of the authors of this commentary (Dr. Williams) is currently conducting clinical trials of Internet-based interventions for rural patients with fibromyalgia. While promising, these newer service delivery modalities need to be evaluated for efficacy, adherence, and practicality.

When Is Management an Acceptable Alternative to a Cure?

No longer do patients with diabetes expect medications to cure the condition. A vast and productive educational campaign has reshaped expectations, drawing together scientific understanding of the condition, responsible and realistic treatment options, and patients' expectations. A similar approach is needed in the management of CNP.

When talking with a colleague about why interventional approaches were chosen over rehabilitation for patients with CNP, my colleague replied that he did not wish to deprive patients of an opportunity to "treat their pain." Along with the desire to offer a cure, one needs to consider that interventional approaches may have undesirable iatrogenic side effects. For example, increased pain and physiological impairment are known risks for nerve blocks. Repeat surgeries are common for disc pathology, and implantable devices are costly temporary solutions for CNP. Similarly, a patient who has undergone a lengthy series of failed interventional procedures may view rehabilitation as a "last straw" for a hopeless case rather than as the appropriate intervention for their type of pain and associated symptoms. Bringing CPPs into the picture earlier rather than later in the course of treatment would help to reduce unnecessary costs and bolster an already impressive array of efficacy studies for CPPs.

References

1. Beattie PF, Meyers SP, Stratford P, Willard RW, Hollenberg GM: Associations between patient report of symptoms and anatomic impairment visible on lumbar magnetic resonance imaging. Spine 25:819-828, 2000

2. Block AR: Presurgical Psychological Screening in Chronic Pain Syndromes: A Guide for the Behavioral Health Practitioner. Mahwah, NJ: Lawrence Erlbaum Associates, 1996

3. Boden SD, Davis DO, Dina TS, Patronas NJ, Wiesel SW: Abnormal magnetic-resonance scans of the lumbar spine in asymptomatic subjects: A prospective investigation. J Bone Joint Surg Am 72:403-408, 1990

4. Dubner R, Ren K: Brainstem mechanisms of persistent pain following injury. J Orofac Pain 18:299-305, 2004

5. Flor H, Fydrich T, Turk DC: Efficacy of multidisciplinary pain treatment centers: A meta-analytic review. Pain 49:221-230, 1992

6. Geisser ME, Roth RS: Knowledge of and agreement with pain diagnosis: Relation to pain beliefs, pain severity, disability, and psychological distress. J Occup Rehabil 8:73-88, 1998

7. Geisser ME, Wiggert EA, Haig AJ, Colwell MO: A randomized, controlled trial of manual therapy and specific adjuvant exercise for chronic low back pain. Clin J Pain 21:463-470, 2005

8. Greenberg JO, Schnell RG: Magnetic resonance imaging of the lumbar spine in asymptomatic adults: Cooperative study-American Society of Neuroimaging. J Neuroimaging 1:2-7, 1991

9. Haldorsen EMH, Grasdal AL, Skouen JS, Risa AE, Kronholm K, Ursinet H: Is there a right treatment for a particular patient group? Comparison of ordinary treatment, light multidisciplinary treatment, and extensive multidisciplinary treatment for long-term sick-listed employees with musculoskeletal pain. Pain 95:49-63, 2002

10. Millard RW, Wells N, Thebarge RW: A comparison of models describing reports of disability associated with chronic pain. Clin J Pain 7:283-291, 1991

11. Romanelli P, Esposito V: The functional anatomy of neuropathic pain. Neurosurg Clin N Am 15:257-268, 2004

12. Tong HC, Williams JC, Haig AJ, Geisser ME, Chiodo A: Predicting outcomes of epidural injections for sciatica. Spine J 3:430-434, 2003

13. Turk DC, Loeser JD, Monarch ES: Chronic pain: Purposes and costs of interdisciplinary pain rehabilitation programs. Trends Evidence-Based Neuropsychiatry 4:64-69, 2002

14. Turk DC, Okifuji A, Scharff L: Chronic pain and depression: Role of perceived impact and perceived control in different age cohorts. Pain 61:93-101, 1995

15. Turk DC, Rudy TE, Kubinski JA, Zaki HS, Greco CM: Dysfunctional patients with temporomandibular disorders: Evaluating the efficacy of a tailored treatment protocol. J Consult Clin Psychol 64:139-146, 1996

16. Vlaeyen JWS, Kole-Snidjers AMJ, Rotteveel AM, Rvesink R, Heuts PHTG: The role of fear of movement/(re)injury in pain disability. J Occup Rehabil 5:235-252, 1995

17. Weishaupt D, Zanetti M, Hodler J, Boos N: MR imaging of the lumbar spine: Prevalence of intervertebral disk extrusion and sequestration, nerve root compression, end plate abnormalities, and osteoarthritis of the facet joints in asymptomatic volunteers. Radiology 209:661-666, 1998

Is acupuncture more effective than sham acupuncture in relieving pain in patients with low back pain?

Original article Brinkhaus B *et al.* (2006) Acupuncture in patients with chronic low back pain. *Arch Intern Med* **166:** 450–457

SYNOPSIS

KEYWORDS acupuncture, alternative medicine, low back pain

BACKGROUND

Chronic low back pain (CLBP) affects a large number of patients, and has a very high financial impact, including expenses incurred on the health system through disability and on society through loss of productivity. Although many different treatments have been used to reduce pain in CLBP, patients often resort to alternative therapies, such as acupuncture.

OBJECTIVE

The object of this study was to compare the efficacy of acupuncture with that of minimal acupuncture and that of no acupuncture in patients with CLBP.

DESIGN AND INTERVENTION

This was a randomized, controlled, multicenter trial. Patients aged 40–75 years, with a clinical diagnosis of CLBP (duration >6 months) and average pain intensity greater than 40 on a 100 mm visual analogue scale in the week before treatment initiation, were randomly allocated to treatment with acupuncture or minimal acupuncture (superficial needling at nonacupuncture points), or to a waiting list (control group). Acupuncture and minimal acupuncture treatments were administered by specialized acupuncture physicians, and consisted of 12 sessions per patient over 8 weeks. Patients completed standardized questionnaires at baseline and at 8, 26, and 52 weeks after randomization. Patients with protrusion or prolapse of intervertebral discs, radicular pain, or low back pain caused by inflammatory or autoimmune disease were excluded from this trial. Analysis was by intention to treat.

OUTCOME MEASURES

The primary outcome measure of this study was improvement in pain, as measured by a 100 mm visual analog scale.

RESULTS

In total, 298 patients (67.8% female, mean age 59 ± 9 years) participated in this study. By the end of the study, pain intensity decreased by a mean of 28.7 ± 30.3 mm in the acupuncture group, a mean of 23.6 ± 31.0 mm, and a mean of 6.9 ± 22.0 mm in the acupuncture group, minimal acupuncture group and waiting list group, respectively. There was a 5.1 mm difference between the acupuncture group and the minimal acupuncture group (95% CI –3.7 to 13.9 mm; $P = 0.26$), and a 21.7 mm difference between the acupuncture group and the waiting list group (95% CI 13.9–30.0 mm; $P < .001$). Pain intensity did not differ significantly between the acupuncture and the minimal acupuncture groups at 26 or 52 weeks ($P = 0.96$ and $P = 0.61$, respectively).

CONCLUSION

The authors conclude that acupuncture is more effective in improving pain than no acupuncture treatment in patients with CLBP; however, acupuncture was no more effective than minimal acupuncture.

COMMENTARY

Daniel J Clauw* and Richard E Harris

CLBP is a significant health problem resulting in major medical expenses and disability. Particularly relevant is the paucity of effective treatments for this condition. The study by Brinkhaus *et al.* examines the efficacy of acupuncture in CLBP patients.

The strengths of this investigation were that it was a randomized, controlled trial with a large sample size. This trial required a large-scale research setting with standardization of acupuncture protocols, extensive data collection procedures, and where clinicians had access to a large number of patients with CLBP.

In this study, Brinkhaus and colleagues found that acupuncture significantly reduced pain compared with allocation to a waiting-list control group, but not when compared with a sham intervention (i.e. superficial needling at nonacupuncture points). Although the improvement in primary outcome did not differ in the active-acupuncture and sham-acupuncture groups, 6 of the 12 secondary outcomes were improved to a significantly higher degree in the active-acupuncture group. Interestingly, pain levels also remained low for up to 11 months following treatment in both the active-acupuncture and sham-acupuncture groups.

These findings are not unique to this study. Many acupuncture trials have found that active acupuncture is only marginally more effective than sham acupuncture, if at all.[1] Nonetheless, both sham and active acupuncture typically lead to significant pain reduction in most studies. Critics of acupuncture often view these findings as negative, and suggest that acupuncture is merely working via a placebo effect. But that is a simplistic explanation of an extremely complex issue. For example, a recent study by Kaptchuk *et al.* supports the notion that "not all placebos are created equally", by demonstrating that sham acupuncture was more effective at treating arm pain than a placebo sugar pill was.[2] These and other data raise important clinical questions regarding the nature of the placebo effect, and perhaps even challenge the negative bias regarding placebo responses.

For example, for almost any trial of an analgesic drug, the magnitude of the placebo effect far exceeds the incremental added value of the drug. This should not be surprising, since there are now overwhelming data that suggest that the placebo effect is very real and has strong neurobiological underpinnings.[3] For example, if a trial (not yet performed) demonstrated that active acupuncture was a slightly more efficacious analgesic than sham acupuncture, and that both were more efficacious than a sugar pill, wouldn't this lead to the conclusion that both active and sham acupuncture were both efficacious, especially if the clinical condition being studied were as difficult to treat as CLBP?

Acupuncture is one of many complementary and alternative therapies that are clearly 'effective' (i.e. work in clinical practice) but cannot always be shown to be 'efficacious' (i.e. work in randomized trials with an appropriate placebo-control group). This might be because we often test these therapies against sham interventions that are not inert, and have very powerful effects of their own. In light of this, clinicians and patients need to decide whether these treatments have utility, and researchers need to be more cognizant of designing their trials so that the results can be appropriately interpreted.

References

1 Ezzo J *et al.* (2000) Is acupuncture effective for the treatment of chronic pain? A systematic review. *Pain* **86:** 217–225

2 Kaptchuk TJ *et al.* (2006) Sham device v inert pill: randomised controlled trial of two placebo treatments. *BMJ* **332:** 391–397

3 Benedetti F *et al.* (2005) Neurobiological mechanisms of the placebo effect. *J Neurosci* **25:** 10390–10402

DJ Clauw is a Professor of Medicine, the Director of the Chronic Pain and Fatigue Research Center and the Center for the Advancement of Clinical Research, and the Assistant Dean of Clinical and Translational Research, and RE Harris is a Research Investigator at the University of Michigan, in Ann Arbor, MI, USA.

Acknowledgments
The synopsis was written by Jasmine Farsarakis, Associate Editor, Nature Clinical Practice.

Competing interests
The authors declared they have no competing interests.

Correspondence
University of Michigan
Medical School
Division of Rheumatology
Department of Medicine
24 Frank Lloyd Wright Drive
PO Box 385
Ann Arbor
MI 48106
USA
dclauw@med.umich.edu

Received 19 April 2006
Accepted 19 May 2006
www.nature.com/clinicalpractice
doi:10.1038/ncprheum0227

PRACTICE POINT
Acupuncture is an effective treatment for chronic low back pain, although further clinical trials are warranted

ARTHRITIS & RHEUMATISM
Vol. 54, No. 12, December 2006, pp 3725–3727
DOI 10.1002/art.22260

Arthritis & Rheumatism

An Official Journal of the American College of Rheumatology
www.arthritisrheum.org and www.interscience.wiley.com

EDITORIAL

A Different Type of Procedure for a Different Type of Pain

Michael C. Hsu and Daniel J. Clauw

In a randomized, placebo-controlled trial described in this issue of *Arthritis & Rheumatism*, Fregni and colleagues studied the effect of transcranial direct current stimulation (tDCS) on pain and quality of life in patients with fibromyalgia (1). These investigators observed that this noninvasive approach was safe and effective for the short-term treatment of fibromyalgia-associated pain. The study also highlights the rapid movement toward neuromodulatory treatment of chronic pain, which requires a paradigm shift in how we think of chronic pain and its management.

The use of various procedures to treat pain is certainly nothing new. For centuries, many procedures have been performed to ameliorate the "source" of pain and typically have been aimed at eliminating peripheral inflammation or repairing peripheral tissue. Some of these procedures work well (e.g., hip replacement surgery), while others have widespread use even though they have not been shown to be efficacious when formally tested in randomized controlled trials. For example, recent systematic reviews revealed only limited evidence, if any, for the long-term therapeutic benefits (compared with placebo) of facet joint injections, extracorporeal shock wave therapy for lateral elbow pain, or corticosteroid injections for shoulder capsulitis, rotator cuff tendonitis, and lateral epicondylitis (2–5). Moreover, procedures aimed at stabilizing or fusing vertebrae or joints have shown limited success in treating pain, and only in highly selected patients (6,7).

The failure of peripherally directed procedures to treat many types of pain is consonant with our current understanding that not all chronic pain is attributable to peripheral damage or inflammation, as measured, for instance, radiographically. In patients with osteoarthritis, there is little relationship between the degree of joint space narrowing and the degree of pain (8). In the setting of low back pain, structural abnormalities on magnetic resonance imaging and discography have only a weak association with back pain episodes and no association with disability or future medical care (9). In fact, in nearly any disease there is a poor relationship between an individual patient's level of pain and the extent or degree of peripheral damage or inflammation that can be documented on objective testing.

We are beginning to understand why such discrepancies may occur. In addition to peripheral or nociceptive pain due to damage or inflammation, there are (at least) 2 other mechanistically distinct types of chronic pain, and these may coexist with peripheral pain (10).

Neuropathic pain is a non-nociceptive chronic pain that has been recognized and understood for some time. Although neuropathic pain is usually attributed to damage and subsequent irritability of peripheral nerves, central changes in pain processing constitute a second type of chronic pain in patients with this condition (11).

A third type of chronic pain is caused by disturbances in the central processing of pain, alone rather than in association with identifiable peripheral input or nerve damage. Such conditions have sometimes been included in the category of neuropathic pain, but they have fundamental differences from neuropathic pain and are often termed "central" pain syndromes. Such syndromes include fibromyalgia, irritable bowel syndrome, temporomandibular joint disorder, and idiopathic low back pain (12). The hallmark of these conditions is the evidence of pain amplification occurring in

Michael C. Hsu, MD, Daniel J. Clauw, MD: University of Michigan Medical School, Ann Arbor.

Address correspondence and reprint requests to Daniel J. Clauw, MD, University of Michigan Chronic Pain and Fatigue Research Center, 24 Frank Lloyd Wright Drive, PO Box 385, Ann Arbor, MI 48106. E-mail: dclauw@med.umich.edu.

Submitted for publication August 31, 2006; accepted in revised form September 6, 2006.

the central nervous system, manifest as allodynia (pain in response to normally nonpainful stimuli) and/or hyperalgesia (increased pain in response to normally painful stimuli) on physical examination, that can be corroborated and "objectified" using sensory testing and functional neuroimaging. This pain amplification may be accompanied by psychological factors but can clearly occur independently and is neurobiologically distinct from depression and/or anxiety (13).

We are also beginning to understand the mechanisms behind this "increased gain" in pain and sensory processing systems. For rheumatologists, it is simplest to think of pain and sensory processing systems as being analogous to the immune system. Autoimmune or inflammatory disorders occur because of a regional or systemic imbalance of proinflammatory versus antiinflammatory influences. Similarly, many inhibitory and facilitatory influences on pain processing can act either regionally (at the level of the peripheral nerve or spinal cord) or systemically (at the level of the spinal cord or brain). For example, pain in patients with fibromyalgia might be attributable, in part, to a lack of normal antinociceptive mechanisms, such as a defect in the function of descending inhibitory (analgesic) pathways, and also a possible increase in spinal excitatory activity such as that which occurs in wind-up or central sensitization (14,15). The ultimate proof that these defective central control mechanisms are playing a role in central pain states comes from randomized clinical trials demonstrating that neuroactive compounds that either increase inhibitory activity (e.g., serotonin–norepinephrine reuptake inhibitors) or decrease facilitatory activity (e.g., antiepileptics) can be efficacious in the treatment of fibromyalgia as well as neuropathic pain (16,17).

The report by Fregni and colleagues raises the possibility that we may also be able to reduce pain in patients with these central pain states by transcutaneously electrically stimulating the brain regions that directly or indirectly influence pain processing. In this study, 32 female patients with fibromyalgia were randomized into 3 groups: tDCS of the primary motor cortex (M1), tDCS of the dorsolateral prefrontal cortex (DLPFC), and sham stimulation. Patients in the 2 active-treatment arms received a constant 2-mA current, 20 minutes daily for 5 consecutive days, while patients in the sham group received only 30 seconds of stimulation of M1 each day. Fregni et al observed a significant decrease in pain (as measured by visual analog scale, clinician's global assessment, and patient's global assessment) in the M1 group compared with the sham group. In contrast, patients in the DLPFC group, who received the same magnitude of electrical stimulation but in a different brain region, had no clinical improvement, making it much less likely that the observed effect in the M1 group was a placebo effect. Pain reduction in the M1 group continued through the 21-day followup period, and no significant side effects were associated with tDCS compared with sham treatment.

In a separate study, these investigators also observed that tDCS had analgesic properties for the central pain of spinal cord injury (18). A similar treatment, transcranial magnetic stimulation (TMS), has been more widely studied and used to stimulate neural regions noninvasively and has analgesic properties in both healthy individuals and patients with chronic pain (19). The mechanisms by which these treatments work are not yet precisely understood, but presumably these treatments are either stimulating inhibitory pathways, such as known endogenous analgesic pathways, or reducing facilitatory activity.

The results of this study, if confirmed by other investigators, suggest an alternative mode of therapy for patients with fibromyalgia or other central pain syndromes. Other neurostimulatory therapies, such as deep brain stimulation (20), spinal cord stimulation (21), and vagus nerve stimulation (22), have also shown promising efficacy in decreasing pain and improving quality of life in selected groups of patients with chronic pain. Although implantable neurostimulatory devices are associated with the inherent risk of complications such as (implant-site) infection and hardware failure, tDCS and TMS have the advantage of being both noninvasive and easily transferable between sites and may obviate the need for invasive neuromodulatory procedures. At a minimum, these techniques will help in the selection of appropriate candidates and appropriate sites for implantation of neurostimulatory devices.

It will take some time before we determine the precise role for these types of therapy in patients with fibromyalgia. In the meantime, the study by Fregni et al provides further evidence that fibromyalgia is associated with abnormal neural activity, and that therapy directed toward these underlying mechanisms can have a specific and clinically meaningful effect on symptoms.

REFERENCES

1. Fregni F, Gimenes R, Valle A, Ferreira M, Rocha R, Natalle L, et al. A randomized, sham-controlled, proof of principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia. Arthritis Rheum 2006;54:3988–98.
2. Boswell MV, Colson JD, Spillane WF. Therapeutic facet joint

interventions in chronic spinal pain: a systematic review of effectiveness and complications. Pain Physician 2005;8:101–14.
3. Bernstein RM. Injections and surgical therapy in chronic pain. Clin J Pain 2001;17(4 Suppl):S94–104.
4. Smidt N, Assendelft WJ, van der Windt DA, Hay EM, Buchbinder R, Bouter LM. Corticosteroid injections for lateral epicondylitis: a systematic review. Pain 2002;96:23–40.
5. Buchbinder R, Green SE, Youd JM, Assendelft WJ, Barnsley L, Smidt N. Shock wave therapy for lateral elbow pain. Cochrane Database Syst Rev 2005;4:CD003524.
6. Van Tulder MW, Koes B, Seitsalo S, Malmivaara A. Outcome of invasive treatment modalities on back pain and sciatica: an evidence-based review. Eur Spine J 2006;15 Suppl 1:S82–92.
7. Gibson JN, Waddell G. Surgery for degenerative lumbar spondylosis: updated Cochrane Review [review]. Spine 2005;30:2312–20.
8. Creamer P, Hochberg MC. Why does osteoarthritis of the knee hurt—sometimes? Br J Rheumatol 1997;36:726–8.
9. Carragee EJ, Alamin TF, Miller JL, Carragee JM. Discographic, MRI and psychosocial determinants of low back pain disability and remission: a prospective study in subjects with benign persistent back pain. Spine J 2005;5:24–35.
10. Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med 2004; 140:441–51.
11. Suzuki R, Dickenson A. Spinal and supraspinal contributions to central sensitization in peripheral neuropathy. Neurosignals 2005; 14:175–81.
12. Clauw DJ, Crofford LJ. Chronic widespread pain and fibromyalgia: what we know, and what we need to know. Best Pract Res Clin Rheumatol 2003;17:685–701.
13. Giesecke T, Gracely RH, Williams DA, Geisser M, Petzke F, Clauw DJ. The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort. Arthritis Rheum 2005;52:1577–84.
14. Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain 2005;114:295–302.
15. Staud R, Vierck CJ, Cannon RL, Mauderli AP, Price DD. Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. Pain 2001;91: 165–75.
16. Arnold LM, Keck PE, Welge JA. Antidepressant treatment of fibromyalgia: a meta-analysis and review. Psychosomatics 2000;41: 104–13.
17. Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. JAMA 2004;292:2388–95.
18. Fregni F, Boggio PS, Lima MC, Ferreira MJ, Wagner T, Rigonatti SP, et al. A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. Pain 2006;122:197–209.
19. Johnson S, Summers J, Pridmore S. Changes to somatosensory detection and pain thresholds following high frequency repetitive TMS of the motor cortex in individuals suffering from chronic pain. Pain 2006;123:187–92.
20. Bittar RG, Kar-Purkayastha I, Owen SL, Bear RE, Green A, Wang S, et al. Deep brain stimulation for pain relief: a meta-analysis. J Clin Neurosci 2005;12:515–9.
21. Van Buyten JP. Neurostimulation for chronic neuropathic back pain in failed back surgery syndrome. J Pain Symptom Manage 2006;31(4 Suppl):S25–9.
22. Multon S, Schoenen J. Pain control by vagus nerve stimulation: from animal to man. . .and back. Acta Neurol Belg 2005;105:62–7.

Representing Natural-Language Case Report Form Terminology Using Health Level 7 Common Document Architecture, LOINC, and SNOMED-CT: Lessons Learned

Dale Hunscher[1, 2] BA; Andrew Boyd, MD[3]; Lee A. Green, MD, MPH[5]; Daniel J. Clauw, MD[2, 4]

1. School of Information, University of Michigan, Ann Arbor, MI
2. Center for the Advancement of Clinical Research, University of Michigan Medical Center, Ann Arbor, MI
3. Department of Psychiatry, University of Michigan Medical School, Ann Arbor, MI
4. Department of Internal Medicine, Division of Rheumatology, University of Michigan Medical School, Ann Arbor, MI
5. Department of Family Medicine, University of Michigan Medical School, Ann Arbor, MI

Abstract: Clinicians and biomedical research investigators ordinarily use natural language when describing biomedical concepts and constructs, even in the context of highly structured case report forms. We describe work in progress and lessons learned in translating complex natural-language concepts on case report forms into machine-readable format using the HL7 CDA, LOINC, and SNOMED-CT standards.

Description of the work: Clinicians and biomedical research investigators ordinarily use natural language when describing history, observations, diagnoses, prognoses, therapies, and other biomedical concepts and constructs. Even in the context of a widely used and well-validated case report form, natural language description is often employed. While this generally improves readability by other human being, it makes translation into machine-level semantics much more complicated. This poster describes work in progress on and fully funded by an NIH Roadmap contract under the Broad Agency Announcement BAA-RM-04-23, "Re-Engineering the Clinical Research Enterprise: Feasibility of Integrating and Expanding Clinical Research Networks".

The contract involves creating an automated Honest Broker system that can mediate between heterogeneous clinical care and research data management systems deployed on several University of Michigan Health System resources: the Depression Network's IVR depression monitoring system, M-DOCC; the Cardiovascular Network, consisting of secondary and tertiary care hospitals treating cardiovascular disease throughout Michigan; GRIN, a practice-based research network with a statewide membership of family practices and community clinics; and Velos, a clinical research data management system maintaining deidentified clinical data sets, deployed at the University of Michigan Medical School.

For purposes of electronic data interchange, we created encoding definitions for messages containing data from several case report forms of various types, including the following: SF-12, to assess quality-of-life; PHQ-9, for depression screening; an internally developed form for assessing medication compliance and satisfaction with the quality of care provided by attending physicians and nurses; and a cardiovascular incident report form. The first three consisted of ten to twenty Likert scale questions whose definitions were not included in any standard repository, while the cardiovascular form consisted of well over one hundred fifty questions fitted onto two densely populated pages.

After investigating syntactic options, we chose the Health Level 7 Common Document Architecture (HL7 CDA) as our format for the representation of forms data transmissions. With the permission of Pfizer and the original author of the PHQ-9, we worked with the Regenstrief Institute to include the definition of the PHQ-9 data points in the LOINC database as part of its growing collection of survey instruments. We developed a LOINC-like internally-maintained encoding for the compliance form and SF-12 data points. For internally maintained encoding definitions we obtained ASN.1 standard OIDs with an eye toward the future, when publication of our encoding schemes might be possible and desirable. The cardiovascular form presented a significant translation challenge, since a great many diagnostic, procedural, prognostic, historical, and other clinical data points were included, all of which had terse natural language prompts. After much investigation and experimentation we managed to encode all data points using SNOMED-CT. Along the way we attempted to define best practices for representing common semantic constructs and handling ambiguity using SNOMED-CT and HL7 CDA, which practices are fully described in the poster.

THE JOURNAL OF ALTERNATIVE AND COMPLEMENTARY MEDICINE
Volume 12, Number 10, 2006, pp. 1035–1039

EDUCATION, INITIATIVES, AND INFORMATION RESOURCES

Policy for Therapeutic Acupuncture in an Academic Health Center: A Model for Standard Policy Development

MONICA MYKLEBUST, M.D.,[1] JAMES COLSON, M.D.,[2] JACQUELINE KAUFMAN, Ph.D.,[3] JEFFERY WINSAUER, O.M.D.[4] YU QUIN ZHANG, O.M.D.,[5] and RICHARD E. HARRIS, Ph.D.[6]

ABSTRACT

Acupuncture as a therapeutic modality offers multiple applications. Its effectiveness coupled with its general acceptance by conventional health care professionals makes it one of the first complementary and alternative medicine (CAM) modalities to be incorporated in an integrative approach to care. However, few centers that offer acupuncture have written standard policies to regulate its use. This lack of standard policies may impede provision of quality care, serve as a barrier to cross-institutional data collection and clinical application of that data, and may put health care professionals and institutions at risk when credentialing or malpractice liability has not been clearly addressed. Here we present a policy for acupuncture, created by a diverse group of health care professionals at the University of Michigan Health System. It may function as a generalizable template for standard policy development by institutions incorporating acupuncture.

INTRODUCTION

In 1997, the National Institutes of Health (NIH) Consensus Conference on Acupuncture endorsed acupuncture's effectiveness for several conditions (Table 1) and concluded that sufficient evidence existed to expand its use into conventional medicine.[1] Since that time, a substantial body of literature supporting the effectiveness of acupuncture in multiple conditions has accumulated.[2–8] At the time of the Consensus Conference, acupuncture had already emerged as the complementary and alternative medicine (CAM) therapy with the highest rate of referral and the most credibility among physicians.[9] However, although national standards guide the training and practice of acupuncturists, legislation governing the licensure of acupuncturists varies from state to state and from institution to institution.

A query of 39 randomly chosen academic health centers in 2005 found that although 23 offered CAM modalities, most commonly including acupuncture, none had written policies addressing credentialing or malpractice liability.[10] After an NIH-funded survey that showed significant variability in the credentialing of alternative providers within academic health centers, Nedrow called for consideration of consistent criteria for credentialing, malpractice liability, and consent.[11] After his survey of 19 integrative health centers noting vastly different policies concerning CAM providers, Cohen et al. concluded that the current environment creates significant impediments to the delivery of consistent care and the evaluation of the safety and efficacy of

[1]University of Michigan Integrative Medicine Clinical Services, Department of Family Medicine, University of Michigan, Ann Arbor, MI.
[2]Department of Anesthesia, University of Michigan, Ann Arbor, MI.
[3]Department of Physical Medicine and Rehabilitation, University of Michigan, Ann Arbor, MI.
[4]Rochester, MI.
[5]Canton, MI.
[6]Department of Internal Medicine, University of Michigan, Ann Arbor, MI.

Table 1. National Institutes of Health Consensus Panel on Acupuncture

Well-demonstrated evidence of effectiveness	*Potentially useful*
Chemotherapy-induced nausea	Addiction
Dental pain	Asthma
Nausea of pregnancy	Carpal tunnel syndrome
Postoperative nausea	Epicondylitis
	Fibromyalgia
	Headache
	Low-back pain
	Menstrual cramps
	Stroke rehabilitation

From ref. 1.

CAM.[12] These authors suggest that a national consensus approach for development of standard guidelines that support provision of CAM services may be justified.

In this paper, we present a policy for therapeutic acupuncture created within an academic health center. Our results may function as a generalizable template for standard policy development by institutions incorporating this therapy. A standardized policy for acupuncture may serve to support provision of high-quality care while decreasing the risk to health care professionals and institutions. It may also serve to promote successful integration of this therapy within conventional health care settings, thus meeting the rising demand for this modality by the consumer.

METHODS

Formation of collaborative

Demonstrated effectiveness coupled with increasing acceptance by conventional medicine made acupuncture a priority for incorporation into University of Michigan Integrative Medicine Clinical Services (UMIMCS). However, no institutional policy, procedure, or professional guidelines existed to support the provision of acupuncture. To address this need, individuals affiliated with the University of Michigan Health System (UMHS) possessing diverse backgrounds in acupuncture were invited to work together as the UMIMCS Acupuncture Collaborative (Table 2). The collaborative discussed, debated, and created the policy for therapeutic acupuncture that follows. Its format is consistent with the guidelines for policy development within the University of Michigan.

Process

Using guidelines set up by the National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM), the collaborative initiated discussion pertaining to the safe and effective nature of acupuncture practice. The collaborative met for seven 90-minute sessions wherein consensus was ultimately achieved. This entailed multiple discussions regarding the methods of acupuncture diagnosis and technique.

A goal in creating the policy was to not only guide the introduction of acupuncture as a treatment option, but also to provide a means to facilitate integration of acupuncture with conventional medicine. For example, the language used was familiar yet accurate between both systems and was discussed as a way to educate readers and potentially bridge the gap between providers. Our discussion of the use of Traditional Chinese Medicine terminology versus conventional medical terminology for patient diagnosis and treatment choices reflected previously described differences between physician and nonphysician acupuncturists.[13] Input from the diverse perspectives of the collaborative ensured rich discussion and promised the development of a policy with broad acceptability.

NCCAOM guidelines were used as the basis for initial discussions regarding the safe and effective practice of acupuncture. A requirement of single-use sterile needles was

Table 2. UMIMCS Acupuncture Collaborative

Member	*Professional background*	*Acupuncture background*
MM	M.D., family medicine, integrative medicine fellowship	Education in theory and history Personal and clinical experience
JC	M.D., anesthesiology/pain medicine	Acupuncture training: Acupuncture Foundation of Canada Institute
JK	Ph.D., psychology/neuropsychology and neurophysiology	Informally educated on acupuncture application and research
JW	Ph.D. (China)	Oriental Medical Doctor (O.M.D.) training: Midwest College for the Study of Oriental Medicine
YZ	M.D., (China) ENT, Surgery, head and neck radiation oncology	Physician and O.M.D. training: University of Shanghai, China
RH	Ph.D. molecular biology	Involved in acupuncture research Acupuncture training: Maryland Institute of Traditional Chinese Medicine

UMIMCS, University of Michigan Integrative Medicine Clinical Service; ENT, ear-nose-and-throat.

easily agreed upon. Because variability exists among schools of acupuncture regarding point selection for the same condition, defining appropriate acupuncture point locations was not so easy for the collaborative to agree on and was thought best left up to the individual acupuncturist. In order to create broad guidelines, mechanisms permitting employees of an institution as well as contract employees to perform acupuncture were included.

This policy is intended to be universally applicable, with modest modifications by each institution to create the best fit. For example, institutional guidelines stating specific language and format for policy development may vary, and it is recommended that readers investigate such guidelines at their local institutions. Also, the exact process for approval of such a policy varies. After completion by the collaborative, our document was presented to legal counsel for approval before being sent to the Office of Clinical Affairs for consideration of formal adoption.

RESULTS (CONSOLIDATED DOCUMENTS)

Therapeutic acupuncture clinical policy and procedure

I. Policy Statement

It shall be the policy of the University of Michigan Health System (UMHS) that acupuncture practitioners with appropriate qualifications may practice acupuncture as a complementary modality to conventional care for various health conditions.

II. Policy Purpose

The purpose of this policy is to describe the clinical application of acupuncture within the University of Michigan Health System.

III. Definitions

Definition of acupuncture

Acupuncture is the insertion of single-use, disposable, sterile, fine-gauge, solid needles into specific body locations (acupuncture points). Each point is needled to a varying depth and angle relative to body location. The diagnostic and pathophysiologic metaphors of Traditional Chinese Medicine, of which acupuncture is a part, are an internally coherent set of theories based on close clinical observation, auscultation, olfaction, inquiries, and palpation; these techniques have been used for millennia. Science has yet to come to a conclusive answer as to how acupuncture works. Historical theories of acupuncture focus on vital energy or *qi* that flows through a system of channels or meridians throughout the body. Blockage of the flow is considered pathologic, and needling is thought to restore harmonic balance of *qi* flow. Regardless of its mechanism of action, acupuncture has been shown to be effective in multiple clinical trials.

Acupuncture indications

An NIH consensus panel and the World Health Organization have approved acupuncture for multiple conditions (Table 1).

IV. Credentials

Therapeutic acupuncture practitioner qualifications

Practitioners must hold a current certification with the NCCAOM. This examination involves demonstration of sterile needle technique and knowledge of Traditional Chinese Medicine theories. In addition, acupuncturists must follow the Code of Ethics and Commitments to the Patient, Profession, and Public as outlined by NCCAOM.

Applicants must possess knowledge and practical application of clinical acupuncture. These requirements must be fulfilled through one of the following:

(1) Graduation from an accredited Oriental Medical institution
(2) Possession of either a M.D. or D.O. with at least 600 hours of accredited training and experience with clinical acupuncture
(3) Completion of an apprenticeship with an experienced acupuncturist.

Practitioners must have experience working in a health care facility, be comfortable working with, and be knowledgeable about conventional medical terminology, diagnosis, and therapies.

Nonphysician practitioners must have a minimum of 2 years' experience as an acupuncturist beyond formal training.

Practitioner must provide evidence of training in patient confidentiality including Health Insurance Portability and Accountability Act of 1996 (HIPAA) privacy training provided by UMHS. They must also demonstrate an understanding of the importance of patient privacy and sign the UMHS Confidentiality Agreement.

Practitioners must provide three references: (1) character; (2) professional; (3) client.

Practitioners must sign an independent practitioner agreement if not an employee of UMHS.

Practitioners must have adequate malpractice insurance.

V. Policy Standards

Referral procedures

The practice will be based on physician referral.

Contraindications and cautions

Contraindication and precaution considerations for acupuncture treatment include special consideration of patients with existing nerve damage, bleeding, and infection risks.

Documentation of treatment

Individualized diagnosis, treatment protocol, and consent will be documented using standard documentation format and provided to the patient's record.

Professional standards and ethics

The acupuncture practitioner will know, understand, and abide by the standards of practice and ethics put forward by the NCCAOM and the professional acupuncture association to which the practitioner belongs.

The acupuncture practitioner will meet the above UMIMCS Therapeutic Acupuncture Practitioner Qualifications and UMHS credentialing requirements.

VI. Therapeutic Acupuncture Consent

I understand and agree:

that I have been evaluated by an acupuncture practitioner, who is not employed by, credentialed by, or in any way associated with the University of Michigan. This practitioner is an independent practitioner and the University of Michigan, its faculty, staff, agents, and employees are not responsible for anything the acupuncture practitioner does or fails to do.

(Alternative: that I have been evaluated by an acupuncture practitioner who is an employee of the University of Michigan.)

The evaluation involved taking a personal health history, clinical observation, and examination. After this examination, a specific treatment plan has been developed with my full understanding, cooperation, and consent. This plan involves the insertion of sterile single-use needles into specified places in my body.

that I have been told the potential benefits of this therapy including: _____

and have been told the possible side effects of this therapy, which can include:

Minor bleeding/bruising
Infection
Fainting
Nerve or tissue injury
Worsening of my condition or no benefit from therapy
Additional side effects: _____

I understand that alternatives to this approach to my condition include:

_____

_____

I have been given an opportunity to ask questions and have had those questions answered to my satisfaction.

I know that acupuncture is designed to be a complementary therapy and is not a substitute for conventional medical treatment.

I know that prior to initiation of any therapy, a referral from my health care provider is required.

I know that by signing this form, I am giving my consent to receive the specific therapy as discussed and agreed upon with the practitioner.

Statement of Consent:

I confirm that I have read and understood the above information, and I consent to having the agreed upon acupuncture treatment described above. I understand that I can decide to discontinue this treatment at any time.

Patient Signature:	Date:
Practitioner Signature:	Date:

VII. Procedures/actions

Patient consultation

Consultation is initiated by physician referral. Prior to an initial treatment, the patient will complete a comprehensive medical health history form. During the consultation, an evaluation and physical examination will be conducted by the acupuncture practitioner. The physical examination will incorporate various aspects of clinical observation derived from both conventional and acupuncture methodology including but not limited to pulse evaluation, auscultation, olfaction, and manual examination of the body. Information from both conventional medicine and Traditional Chinese Medicine are integrated into the evaluation and treatment plan.

Acupuncture treatment

The acupuncture treatment will be guided by the evaluation and treatment plan determined by patient consultation. As a result of the clinical inquiry conducted, the patient will present in a symbolic pattern. The acupuncturist will then apply acupoints that are applicable to the perceived pattern in the form of a treatment strategy. The treatment plan will be discussed with the patient prior to treatment initiation. Patient consent will be obtained and documented at this time. The patient will be positioned appropriately with consideration to patient comfort and privacy. Sterile techniques will be used at all times. Single-use, disposable, sterile needles are used. Upon insertion, the needle is manipulated until the patient experiences a *de qi* sensation, which is a localized warming, spreading, or numbing sensation. The needles are left in place for between 15 and 30 minutes. Needles will be disposed of in appropriate sharps containers. Needles will never be reused.

CONCLUSIONS

The use of CAM therapies continues to increase. As studies validate effectiveness, mechanisms must be established to guide safe and responsible integration of these therapies

into patient care. Recent studies show that health centers lack standard policies regarding the provision of CAM therapies despite their institutional use of such therapies.[12]

The policy presented here was created by a diverse group of health care professionals whose grassroots approach provided the opportunity to write materials that represent a wide range of ideas and perspectives, and to get buy-in at many levels. For this reason, this document may be especially generalizable in supporting the integration of therapeutic acupuncture within other health care centers.

Because national criteria already exist for some aspects of acupuncture practice (for example NCCAOM), our discussions were informed by these criteria and they served as a foundation for our process. However, there are unique considerations for the practice of acupuncture in a conventional health care center. Practitioners need to be knowledgeable about conventional medical terminology, diagnosis, and therapies outside the scope of acupuncture alone. They need to use language understood by a conventional medical team when describing their findings and treatment, and when documenting in the chart. Within our health care center, the acupuncturist must also meet institutional requirements for patient care, such as HIPAA privacy training.

Generalizable aspects of the policy include the policy statement, purpose, definition of acupuncture and its indications, credentialing criteria, contraindications, and consent. However, some aspects of our document may need to be modified based on institution procedures. For example, the policy format must be consistent with guidelines for policy development within each institution. Referral procedures may vary because our policy requires a physician referral. Furthermore, documentation specifics such as who is allowed access to patient charts may also vary across institutions. Finally, a specific description of acupuncture consultation and treatment may also differ. It is worth noting that at the time of this writing, several states, including Michigan, are on the cusp of passing acupuncture legislation regulating the practice of acupuncture. If your state licenses acupuncturists, the phrase "and be state licensed" should be added to section IV, paragraph 4 of the policy document, which refers to nonphysician practitioners.

Presented is a detailed policy for the implementation of therapeutic acupuncture in an academic health care center. It is may be easily modified and used as a template for standard policy development by institutions incorporating acupuncture. Standard policy serves to support the provision of high-quality care, limit liability, and facilitate data collection. Additionally, this policy encourages further dialogue among conventional, CAM, and integrative health care professionals regarding the indications for, process of integrating, and outcomes of providing acupuncture. Further development of standard policy to guide the integration of additional CAM therapies is indicated as the emerging field of integrative medicine expands.

ACKNOWLEDGMENTS

The authors wish to thank Richard Hammerschlag, Ph.D., for his helpful suggestions on this manuscript.

REFERENCES

1. Anonymous. NIH Consensus Conference. Acupuncture. JAMA 1998;280:1518–1524.
2. Birch S, Hammerschlag R, Berman BM. Acupuncture in the treatment of pain. J Altern Complement Med 1996;2:101–124.
3. Mayer DJ. Biological mechanisms of acupuncture. Prog Brain Res 2000;122:457–477.
4. Berman BM, Lao L, Langenberg P, et al. Effectiveness of acupuncture as adjunctive therapy in osteoarthritis of the knee: A randomized, controlled trial. Ann Intern Med 2004;141:901–910.
5. Witt C, Brinkhaus B, Jena S, et al. Acupuncture in patients with osteoarthritis of the knee: A randomised trial. Lancet 2005;366:136–143.
6. Brinkhaus B, Witt CM, Jena S, et al. Acupuncture in patients with chronic low back pain: A randomized controlled trial. Arch Intern Med 2006;166:450–457.
7. Linde K, Streng A, Jurgens S, et al. Acupuncture for patients with migraine: A randomized controlled trial. JAMA 2005; 293:2118–2125.
8. Melchart D, Streng A, Hoppe A, et al. Acupuncture in patients with tension-type headache: Randomised controlled trial. BMJ 2005;331:376–382.
9. Astin JA, Marie A, Pelletier KR, et al. A review of the incorporation of complementary and alternative medicine by mainstream physicians. Arch Intern Med 1998;158:2303–2310.
10. Cohen MH, Sandler L, Hrbek A, et al. Policies pertaining to complementary and alternative medical therapies in a random sample of 39 academic health centers. Altern Ther Health Med 2005;11:36–40.
11. Nedrow A. Status of credentialing alternative providers within a subset of U.S. academic health centers. J Altern Complement Med 2006;12:329-335.
12. Cohen MH, Hrbek A, Davis RB, et al. Emerging credentialing practices, malpractice liability policies, and guidelines governing complementary and alternative medical practices and dietary supplement recommendations: A descriptive study of 19 integrative health care centers in the United States. Arch Intern Med 2005;165:289–295.
13. Kalauokalani D, Cherkin DC, Sherman KJ. A comparison of physician and nonphysician acupuncture treatment for chronic low back pain. Clin J Pain 2005;21:406–411.

Address reprint requests to:
Richard E. Harris, Ph.D.
Department of Internal Medicine
University of Michigan
Domino's Farms 0737
Ann Arbor, MI 40106

E-mail: reharris@med.umich.edu

Predictors of Exercise Compliance in Individuals with Gulf War Veterans Illnesses: Department of Veterans Affairs Cooperative Study 470

Guarantor: DeAnna L. Mori, PhD
Contributors: DeAnna L. Mori, PhD*; Stephanie Sogg, PhD†; Peter Guarino, MPH‡; James Skinner, PhD§; David Williams, PhD¶; Andre Barkhuizen, MD‖; Charles Engel, MD MPH**; Daniel Clauw, MD¶; Sam Donta, MD††; Peter Peduzzi, PhD‡

Although the health benefits of exercise for individuals with Persian Gulf War veterans illnesses (GWVI) are documented, many of these individuals do not exercise regularly enough to obtain benefits. The purpose of this study was to investigate factors predicting exercise compliance among individuals with GWVI in a multicenter, randomized, clinical trial. Participants were 1,092 veterans who reported at least two of the following cardinal symptoms of GWVI: (1) fatigue, (2) musculoskeletal pain, and (3) cognitive problems. Participants received exercise alone or exercise and cognitive-behavioral therapy. The overall level of compliance was relatively low during the exercise treatment phase (46.2%) and decreased by one-half during the follow-up period (23.0%). Predictors of compliance during treatment included less pain and greater age, motivation, and body mass index. Predictors of compliance during the follow-up period included less pain and greater age. The results highlight factors that affect adoption and maintenance of physical activity in a population with GWVI.

Introduction

The health benefits associated with exercise have been well described. Exercise is one of the best predictors of successful weight loss maintenance and has been shown to decrease the risk of developing many chronic diseases.[1–4] Furthermore, exercise has been successfully used to treat symptoms associated with many chronic medical conditions, including chronic fatigue syndrome[5] and fibromyalgia.[6–8] Exercise has also been shown to be effective in reducing some symptoms associated with Persian Gulf War veterans illnesses (GWVI).[9]

In addition to the physiological benefits associated with exercise, there are psychological benefits, including reductions in anxiety and depression,[10] positive effects on mood and psychological well-being,[11,12] increased quality of life for patients with medical conditions,[13,14] and a catalyst for other positive health behaviors.[15] These benefits have particular relevance for people with GWVI or other chronic physical problems, because psychological symptoms often occur with these illnesses.

Despite the well-documented benefits of exercise, ≥60% of adults in the United States do not exercise regularly enough to obtain these benefits.[16] Rates of inactivity are particularly high among older adults, women, people with less education, and people of ethnic minorities.[16,17] Psychosocial variables inversely associated with exercise adoption and maintenance include perceived barriers, lack of perceived behavioral control, lack of self-efficacy, and negative affect.[16] Many adults begin exercise programs, but more than one-half of those who do engage in regular physical activity stop exercising within 3 to 6 months.[18,19]

Although more is being learned about the adoption and maintenance of exercise behavior, many questions remain unanswered.[20,21] In particular, there is a need for more knowledge about maintenance of physical activity for people with chronic illnesses because it has been suggested that this population is less likely to engage in moderate or vigorous activity than are people without chronic illnesses,[16] and long-term exercise compliance in this population is poor.[22] This is an important area of investigation because the benefits of physical exercise for many chronic conditions are well substantiated,[9,16] and exercise is increasingly becoming an integral part of medical treatment recommendations.[23] Although the health benefits of exercise are substantial, the benefits will not be sustained unless the person continues to exercise in an ongoing regular manner.[20] This is highly relevant in evaluating the factors associated with exercise maintenance for patients with GWVI, which is characterized by chronic pain, fatigue, and cognitive problems.

In light of these findings, this substudy was conceptualized with the objective of exploring the demographic, medical, and psychosocial variables that affect exercise compliance and maintenance in a population of patients with GWVI. This is an important area of investigation because this population has multiple risk factors for poor exercise compliance. For example, individuals afflicted with GWVI have high rates of negative affect,[9] which is associated with poor compliance with exercise. Furthermore, the physical symptoms (pain and fatigue) and cognitive symptoms (poor concentration, attention, and memory) associated with the illness can create barriers to exercise or decrease the patient's sense of self-efficacy, which can lead to poor exercise compliance. By prospectively assessing these fac-

*Veterans Affairs Boston Healthcare System, Psychology Service, Boston, MA 02130.
†Weight Center, Massachusetts General Hospital, Boston, MA 02114.
‡Cooperative Studies Program, Coordinating Center, VA Connecticut Healthcare System, West Haven, CT 06516.
§Department of Kinesiology, Indiana University, Bloomington, IN 47405.
¶Chronic Pain and Fatigue Research Program, University of Michigan, Ann Arbor, MI 48106.
‖Oregon Health and Science University, Portland, OR 97239.
**Department of Psychiatry, Uniformed Services University of the Health Sciences, Bethesda, MD 20814-4799.
††Department of Medicine, Boston University School of Medicine, Boston, MA 02118.

The opinions of Dr. Engel expressed herein are his own and should not be construed as the official opinion or position of Walter Reed Army Medical Center, Uniformed Services University, the Department of the Army, or the Department of Defense.

This manuscript was received for review in January 2005 and was accepted for publication in January 2006.

tors that may affect exercise compliance and maintenance in a population of patients with GWVI, we hope to identify a profile of relevant factors that are predictive of success in adhering to a 12-week exercise program and maintaining physical activity over a 9-month follow-up period. Such results should be useful in improving interventions designed to increase exercise compliance, particularly in a chronically ill population with symptoms characterized by pain, fatigue, and cognitive problems.

Methods

Study Design

This investigation was a substudy of Department of Veterans Affairs Cooperative Study 470, a randomized multicenter trial designed to examine the efficacy of cognitive-behavioral therapy (CBT) and aerobic exercise treatment for symptoms of GWVI. The study was conducted in 18 Department of Veterans Affairs and two Department of Defense medical centers located across the United States and included 1,092 veterans who were deployed to the Persian Gulf War and reported at least two of the following three cardinal symptoms of GWVI: (1) fatigue, (2) musculoskeletal pain, and (3) cognitive symptoms (memory, concentration, or attention difficulties). Participants were randomized to one of four treatment arms, namely, (1) aerobic exercise alone, (2) CBT alone, (3) aerobic exercise plus CBT, or (4) usual care. The design and primary results of this study were reported previously.[9,24] This substudy of the larger project was designed to identify predictors of exercise compliance in the groups of veterans who received exercise alone or exercise in combination with CBT.

Treatment Regimens

Aerobic Exercise Alone

A submaximal cycle ergometer exercise test was used to determine each participant's level of physical fitness and to develop exercise prescriptions. The test began at 30 W for 2 minutes, followed by increases of 15 W every 2 minutes until participants reached their submaximal target heart rate [(220 − age) × 0.85]. At the end of each 2-minute cycle, heart rate and blood pressure were recorded and participants were asked to give a rating of perceived exertion (RPE), using the Borg scale.[25] If the target heart rate was not reached, then the test was stopped at an RPE of 17 (very hard).

Heart rates, power outputs, and RPEs at the desired intensities of exercise during the baseline test were used to prescribe exercise on an individual basis for the participants randomized to an exercise treatment group. Heart rate monitoring permitted participants to set their exercise intensity based on how their body responded to exercise. Power outputs were converted to equivalent metabolic energy costs (METS) and allowed participants to select exercises that corresponded to the desired intensity from a wide variety of recreational and occupational activities. RPE ratings allowed participants to modify their activity level depending on how they felt each day.

During the 12-week treatment phase, participants exercised for 1 hour in the presence of the exercise therapist once per week. Therapists instructed participants about exercise, stretching techniques, and activity selection using RPE, heart rate, and METS.[24] Participants were also asked to exercise independently two or three times per week during the 12-week treatment phase and throughout the maintenance phase. Intensity and duration of exercise were gradually increased as tolerated. After the 3- and 6-month follow-up exercise tests, the exercise prescription was modified according to changes in fitness and according to each veteran's reaction to exercise or his or her illness.

Exercise and CBT

In addition to exercise, this treatment group also received CBT. The two aims of CBT for GWVI were to gradually improve physical functioning and to enhance problem-solving skills. The CBT protocol was not designed to directly enhance exercise compliance. Instead, the CBT modules focused on targeting specific physiological and psychological symptoms associated with GWVI. CBT was delivered to groups of three to eight participants. Participants received both 12 one-hour weekly sessions of CBT and the 12 one-hour weekly sessions of aerobic exercise described above.

To ensure the standardization of study procedures, an operations manual was developed and a comprehensive training meeting was conducted with all research personnel before initiation of the study. Also before the study, experts in exercise physiology and CBT provided training for all of the therapists, to ensure the uniformity and quality of the interventions across all sites. The expert consultants also conducted biweekly conference calls for each group, to address any issues and problems. In addition, all sites participated in weekly conference calls with members of the executive study staff from the coordinating center, to review procedures and to address problems.

Baseline and Follow-up Assessments

Participants were evaluated at baseline, 3 months (immediately after the treatment phase), 6 months, and 1 year. Evaluations included a submaximal exercise test and several psychometric instruments, which were administered by a research assistant who was masked to treatment assignment.

Physical and mental functioning was measured with the Veterans Short-Form 36-item questionnaire (V/SF-36).[26–28] The V/SF-36 measures eight domains of physical and mental health functioning. Two summary scores, the physical component summary (PCS) and the mental component summary (MCS), are derived from these eight measures.

Pain was assessed with the short form of the McGill Pain Questionnaire,[29] which measures both the quality of pain (self-reported ratings of the intensity of 15 pain adjectives on a scale of 0–3) and the present and typical intensity of pain overall (self-reported ratings on a scale of 0–10). Three summary scores were computed, namely, sensory pain, affective pain, and present pain. An additional measure, typical level of pain, was obtained by asking participants to record their typical level of pain intensity, using an 11-point scale from 0 (no pain) to 10 (worst possible).

Fatigue was measured with the Multidimensional Fatigue Inventory,[30] a 20-item, self-report questionnaire organized into five categories of fatigue, i.e., general, physical, mental, reduced motivation, and reduced activity. This instrument has been found to be reliable and valid and is widely used in studies of chronic fatigue syndrome and fibromyalgia.[31]

Cognitive symptoms were assessed with the Cognitive Failures Questionnaire,[32] a 25-item instrument measuring subjective perceptions of cognitive impairment. Emotional distress was measured with the Mental Health Inventory, a subscale of the V/SF-36.

The presence of depression and anxiety disorders were identified with the Primary Care Evaluation of Mental Disorders,[33] which consists of a screening questionnaire followed by a structured assessment interview to detect mental disorders common in primary care patients.

The presence of a personality disorder was assessed with the personality disorders scale of the Inventory of Interpersonal Problems.[34] This 47-item scale has strong psychometric properties for distinguishing between patients with "any" versus "no" personality disorder.

During both treatment and maintenance periods, participants were asked to keep a daily log to record the frequency, duration, and intensity of their physical activity. Participants also recorded the method they used to determine the intensity of their exercise (heart rate, perceived exertion, or a chart listing METS for a variety of activities). During the treatment period, the participants reported this information each week to study personnel. During the maintenance period, the study coordinator telephoned participants monthly to collect this information.

Primary Outcome

For the purposes of theses analyses, the primary outcome was defined with a dichotomous measure of exercise compliance (noncompliant versus compliant). Participants were classified as compliant if they reported exercising at their target heart rate, RPE, or METS level an average of three times per week for an average total of 90 minutes per week. This dichotomous measure of compliance was based on the criteria that are typically used to determine whether an individual has successfully adopted physical activity behavior and was chosen because it is consistent with the goal toward which participants were asked to work. Predictors of exercise compliance were measured during two time periods, i.e., the initial 3-month treatment phase and the maintenance phase (4 months to 12 months after randomization).

Statistical Analyses

Baseline characteristics in the exercise-alone and exercise plus CBT arms are presented as means and SDs for continuous measures and as counts and percentages for discrete measures. Univariate logistic regression analysis was initially used to identify a set of factors that were associated with exercise compliance, coded as 1 for compliant and 0 for noncompliant. Four participants who were assigned to exercise alone and who did not have a calculable PCS score were excluded from the analysis. This analysis was performed separately within each exercise arm for the treatment and maintenance phases. Because the resulting sets of predictors were different for the exercise-alone and exercise plus CBT groups, predictors were not determined for the two groups combined. The baseline predictors initially examined were demographic factors (gender, age, race, and education), body mass index, current depressive or anxiety disorder, presence of a personality disorder, current or pending disability claim, and measures of pain, fatigue, cognitive symptoms, PCS, MCS, and emotional distress. Factors that were significant at the 0.10 level were then entered into a multivariate logistic regression model to determine independent predictors of exercise compliance. The final set of independent predictors was selected through backward elimination, using a p value criterion of <0.05 to be retained in the model. This strategy was used because there were too few compliant participants during the maintenance phase to satisfy the criterion of at least 10 outcomes per independent variable included in the full model, as required for backward selection.[35] Results are presented as odds ratios, with corresponding 95% confidence intervals, whenever appropriate. Because all analyses were considered exploratory, no correction for multiplicity was done. SAS version 8.2 software (SAS Institute, Cary, North Carolina) was used for all analyses.

Results

Patient Characteristics

The entry characteristics of those assigned to exercise alone ($N = 265$) and those assigned to exercise plus CBT ($N = 266$) are displayed in Table I. Participants in the two treatment arms were reasonably comparable at baseline.

Compliance with Exercise

Compliance with exercise in the treatment and maintenance phases is displayed in Table II according to treatment arm. Overall, compliance with exercise was nearly two times higher in the treatment phase, compared with the maintenance phase. Compliance tended to be higher in both phases for those assigned to exercise alone (45% and 25%), compared with those assigned to exercise plus CBT (40% and 21%), but the treatment differences were not significant.

Predictors of Exercise Compliance

Exercise-Alone Arm

Table III displays the association of each potential baseline predictor with exercise compliance in both the treatment and maintenance phases. Seven factors were univariately predictive of exercise compliance during the treatment phase, including age, years of education, presence of a personality disorder, and measures of the typical level of pain, affect pain, physical fatigue, and distress. Among these factors, only age and typical level of pain were significant independent predictors of exercise compliance during the treatment phase (Table IV). Increasing age was associated with better exercise compliance, and higher typical levels of pain were associated with poorer exercise compliance. Each increase of 1 year in age increased the odds of adhering by 5%, and each 1-unit increase in the typical level of pain decreased the odds of adhering by 15%. For the maintenance phase, three factors were univariate predictors of exercise compliance (typical level of pain, general fatigue, and physical fatigue); of these, only typical level of pain was an independent predictor of exercise compliance (Table IV). Each 1-unit increase in the typical level of pain measure decreased the odds of adhering by 16%, a finding similar to that found in the treatment phase.

Exercise plus CBT Arm

Significant univariate predictors of exercise compliance during the treatment phase included age, presence of anxiety or

TABLE I

BASELINE CHARACTERISTICS OF STUDY PARTICIPANTS ACCORDING TO TREATMENT ASSIGNED

Characteristic	Exercise (n = 265)	Exercise plus CBT (n = 266)
Age (years)	40.9 ± 8.9	39.9 ± 8.4
Female, n (%)	33 (12.3)	51 (19.2)
Race/ethnicity, n (%)		
Caucasian, non-Hispanic	152 (56.5)	132 (49.6)
African American, non-Hispanic	55 (20.4)	69 (25.9)
Hispanic	56 (20.8)	55 (20.7)
Other	6 (2.3)	10 (3.8)
Education (years)	14.1 ± 1.9	13.9 ± 1.8
V/SF-36 PCS score	34.0 ± 7.5	33.9 ± 7.4
V/SF-36 MCS score	35.8 ± 11.3	37.1 ± 12.4
McGill Short Form (pain scores)		
Sensory pain	13.6 ± 6.8	13.3 ± 7.2
Affective pain	4.3 ± 3.0	4.5 ± 3.2
Pain right now	5.1 ± 2.3	4.9 ± 2.3
Typical level of pain	5.8 ± 2.0	5.6 ± 2.1
Multidimensional fatigue Inventory scores		
General fatigue	16.7 ± 2.9	16.4 ± 3.2
Physical fatigue	15.1 ± 3.3	14.8 ± 3.3
Reduced activity	13.5 ± 3.7	13.4 ± 4.0
Reduced motivation	12.0 ± 3.3	11.8 ± 3.8
Mental fatigue	14.9 ± 3.9	14.9 ± 3.8
Cognitive difficulties		
Cognitive failures Questionnaire score	66.6 ± 18.2	66.8 ± 16.7
V/SF-36 Mental Health Index score	52.4 ± 20.5	53.9 ± 22.0
Depression or anxiety disorder, n (%)	189 (71.3)	181 (68.1)
Personality disorder, n (%)	133 (50.2)	148 (55.6)
Disability or claims pending, n (%)	151 (57.0)	131 (49.3)
Physical fitness		
Body mass index	29.8 ± 4.9	29.0 ± 4.6
Peak heart rate attained (beats per minute)	142.0 ± 17.1	139.9 ± 19.3

Values are means ± SD.

depression, body mass index, MCS, and reduced motivation (Table V). Among these five predictors, only age, body mass index, and reduced motivation were significant independent predictors of compliance in the multivariate analysis (Table VI). Increasing age and body mass index were associated with increased compliance, and reduced motivation was associated with decreased compliance. Each increase of 1 year in age increased the odds of adhering by 4%, and each 1-unit increase in body mass increased the odds by 6%. In contrast, each 1-unit increase in the measure of reduced motivation decreased the odds of adhering by 9%. For the maintenance phase, age and gender were univariately predictive of exercise compliance, but only age was an independent predictor of compliance (Table VI). Similar to the treatment phase, each increase of 1 year in age increased the odds of adhering by 6%.

TABLE II

PARTICIPANT COMPLIANCE WITH EXERCISE ACCORDING TO PHASE AND TREATMENT CONDITION

Treatment Group	N[a]	No. (%) Treatment-Phase Compliers[b]	No. (%) Maintenance-Phase Compliers[b]
Exercise alone	265	119 (44.9)	66 (24.9)
Exercise plus CBT	266	107 (40.2)	56 (21.1)
Total	531	226 (42.6)	122 (23.0)
p[c]		0.28	0.29

[a] N is the number of participants without missing data for each predictor.

[b] Compliance was defined as exercising at the target heart rate, RPE, or METS level an average of 3 times per week and an average total of 90 minutes per week.

[c] For comparison of compliance rates among those assigned to exercise alone vs. those assigned to exercise plus CBT.

Discussion

By prospectively assessing the factors associated with exercise compliance and maintenance in veterans with GWVI, we identified a set of factors that predicted compliance with a 12-week exercise program and maintenance of physical activity over a 9-month follow-up period. Our findings provide some insight into the factors that may affect compliance with exercise treatment and maintenance among people with symptoms of GWVI or other chronic illnesses that are similarly characterized by chronic pain, fatigue, and cognitive problems.

Overall, we found a relatively low rate of compliance with exercise, with only 42.6% of participants complying with exercise recommendations during the initial 12-week treatment phase. This rate of compliance was nearly halved once formal treatment ended, with only 23% of participants exercising at the recommended level. These findings are consistent with previous reports that suggested that more than one-half of people who begin exercise programs stop exercising within 3 to 6 months,[18,19] providing further support for the need to develop methods that enhance long-term exercise maintenance.

The predictors of exercise compliance generally differed in the treatment and maintenance phases in the two treatment arms. In the exercise-alone arm, typical level of pain and age predicted compliance during the treatment phase, whereas only the former predicted compliance during the maintenance phase. Higher levels of pain were related to poorer compliance, presumably because people experiencing more pain would be less inclined to exercise. In contrast, increasing age was related to better compliance but only in the treatment phase. This finding was unexpected and inconsistent with reports that suggested that individuals are less likely to engage in exercise as they get older.[36] This discrepancy might have resulted because our study population was relatively young, with a mean age of ~40 years. Our finding suggests that, in a relatively young population, increasing age is associated with a greater likelihood of exercise compliance, a result that merits further investigation.

In the exercise plus CBT treatment arm, reduced motivation, body mass index, and age were independent predictors of exer-

TABLE III

UNIVARIATE BASELINE PREDICTORS OF EXERCISE COMPLIANCE ACCORDING TO PHASE (EXERCISE-ALONE PARTICIPANTS, $N = 265$)

Predictor	N[a]	Treatment Phase		Maintenance Phase	
		Odds Ratio	p	Odds Ratio	p
Age	265	1.05	0.002	1.02	0.34
Gender	265	1.03	0.95	1.15	0.74
Education	265	1.12	0.09	0.92	0.26
Anxiety/depression	265	0.75	0.29	0.90	0.74
Disability or pending claim	258	0.74	0.29	0.74	0.36
Personality disorder	265	0.62	0.06	0.91	0.75
Body mass index	263	1.01	0.75	1.01	0.77
PCS	265	1.01	0.51	1.03	0.18
MCS	265	1.02	0.12	1.01	0.49
Pain right now	253	0.96	0.46	0.99	0.82
Typical level of pain	264	0.85	0.01	0.84	0.01
Sensory pain	248	0.97	0.16	0.97	0.20
Affect pain	254	0.91	0.04	0.98	0.71
General fatigue	265	0.96	0.37	0.91	0.05
Physical fatigue	265	0.93	0.07	0.93	0.10
Reduced activity	261	1.01	0.75	0.99	0.71
Reduced motivation	261	1.04	0.41	0.98	0.69
Mental fatigue	264	1.02	0.61	0.96	0.21
Cognitive Failures Questionnaire	256	1.00	0.96	1.00	0.60
Distress	265	1.01	0.10	1.01	0.49

Gender (male versus female), personality disorder (present versus absent), and pending disability claim (present versus absent) were analyzed as dichotomous variables, and all other predictors were continuous measures.

[a] N is the number of participants without missing data for each predictor.

TABLE IV

MULTIVARIATE PREDICTORS OF EXERCISE COMPLIANCE ACCORDING TO PHASE (EXERCISE-ALONE PARTICIPANTS)

Predictor	Treatment Phase ($n = 253$)		Maintenance Phase ($n = 264$)	
	Odds Ratio	95% CI	Odds Ratio	95% CI
Typical level of pain	0.85	0.74–0.97	0.84	0.72–0.96
Age (years)	1.05	1.02–1.08		

CI, confidence interval.

cise compliance during the treatment phase, of which only age was an independent predictor during the maintenance phase. As expected, a higher score on the measure of reduced motivation (a dimension of the Multidimensional Fatigue Inventory) was related to poorer compliance with exercise. Level of motivation was not predictive of compliance during the maintenance phase, which could be explained by the likelihood that participants who were experiencing reduced motivation related to fatigue had already dropped out. Surprisingly, we found that an increased body mass index was associated with better exercise compliance during the treatment phase. It is possible that heavier participants were motivated by the prospect of "getting in shape" by exercising regularly. However, a greater body mass index was not predictive of longer-term maintenance of physical activity during the follow-up phase. Similar to what was found in the exercise-alone group, increasing age was related to better compliance during the treatment phase for the exercise plus CBT group but, unlike in the exercise-alone group, it was not a predictor during the maintenance phase. The finding that the predictors were somewhat different between the treatment and maintenance phases of the study in both treatment arms suggests that factors influencing the initial adoption of exercise behavior are somewhat different from those affecting longer-term maintenance of established behavior.

Except for age, the predictors of exercise compliance differed in the two treatment arms. Typical level of pain was a predictor of compliance only in the exercise-alone arm. A possible explanation for this finding is that, although CBT did not directly target exercise compliance, it included a module on behavioral activation and pacing early in the treatment that taught participants how to complete activities without exacerbating pain and fatigue. In contrast, reduced motivation might have had a negative impact on compliance only in the exercise plus CBT group because combined therapy placed more demands on the less-motivated individuals, making it more difficult to comply with therapy. This result is consistent with reports that suggested that compliance may be poorer among people who follow more complex treatment protocols.[37] It is not clear why greater body mass index predicted compliance in the combined treatment group and not in the exercise-alone group. One possible explanation is that the behavioral activation and pacing module in the CBT protocol might have motivated heavier participants by helping them to develop a more realistic and healthy approach to exercise, thereby enhancing their self-efficacy for physical activity.

TABLE V

UNIVARIATE BASELINE PREDICTORS OF EXERCISE COMPLIANCE ACCORDING TO PHASE (EXERCISE PLUS CBT PARTICIPANTS, $N = 266$)

		Treatment Phase		Maintenance Phase	
Predictor	N^a	Odds Ratio	p	Odds Ratio	p
Age	266	1.04	0.005	1.06	0.002
Gender	266	1.56	0.16	1.77	0.10
Education	265	1.09	0.22	1.02	0.83
Anxiety/depression	266	0.62	0.07	0.89	0.72
Disability or pending claim	259	1.26	0.44	1.29	0.46
Personality disorder	266	0.70	0.16	1.08	0.80
Body mass index	265	1.07	0.01	1.04	0.28
PCS	265	0.99	0.43	1.00	0.82
MCS	265	1.02	0.03	1.01	0.57
Pain right now	259	0.96	0.43	0.96	0.56
Typical level of pain	259	0.94	0.31	0.94	0.37
Sensory pain	253	0.98	0.25	1.00	0.98
Affect pain	261	0.95	0.19	1.01	0.82
General fatigue	266	0.97	0.47	1.01	0.92
Physical fatigue	266	0.97	0.40	0.97	0.53
Reduced activity	263	0.98	0.55	1.01	0.77
Reduced motivation	266	0.92	0.01	0.99	0.75
Mental fatigue	265	0.98	0.52	0.99	0.87
Cognitive Failures Questionnaire	257	1.00	0.61	1.00	0.80
Distress	266	1.01	0.51	1.00	0.55

Gender (male versus female), personality disorder (present versus absent), and pending disability claim (present versus absent) were analyzed as dichotomous variables, and all other predictors were continuous measures.

[a] N is the number of participants without missing data for each predictor.

TABLE VI

MULTIVARIATE PREDICTORS OF EXERCISE COMPLIANCE ACCORDING TO PHASE (EXERCISE PLUS CBT PARTICIPANTS)

	Treatment Phase ($n = 265$)		Maintenance Phase ($n = 266$)	
Predictor	Odds Ratio	95% CI	Odds Ratio	95% CI
Age (years)	1.04	1.01–1.08	1.06	1.02–1.09
Body mass index	1.06	1.00–1.12		
Reduced motivation	0.91	0.85–0.98		

CI, confidence interval.

Increasing age was the only common predictor of exercise behavior in both treatment arms, predicting both short-term adoption of behavior and longer-term maintenance in the combined treatment arm and predicting short-term adoption of exercise in the exercise-alone arm. A possible explanation for this finding is that exercise was promoted as a potential treatment for the symptoms associated with GWVI. Thus, younger participants might have been more reluctant to identify with having a "chronic illness," lessening their motivation to participate in an exercise program to reduce symptoms. Perhaps greater compliance could have been achieved among the younger participants if exercise had been promoted with a primary goal of improving fitness, an area for further investigation.

The results from this study highlight factors that may affect the adoption and maintenance of physical activity by individuals with GWVI. This information can be used to help design more effective treatment programs, by addressing issues that may affect compliance with exercise recommendations in this population. This has important clinical implications, because exercise is one of the few treatments that have been shown to effectively address some symptoms of GWVI.

Acknowledgments

We thank Elizabeth Dettmer, PhD, for the input she provided in the development of this substudy.

This research was funded by the Cooperative Studies Program of the U.S. Department of Veterans Affairs Office of Research and Development and the U.S. Department of Defense (Cooperative Study 470).

References

1. Powell KE, Blair SN: The public health burdens of sedentary living habits: theoretical but realistic estimates. Med Sci Sports Exerc 1994; 26: 851–6.
2. Pronk N, Wing RR: Physical activity and long-term maintenance of weight loss. Obes Res 1994; 2: 587–99.
3. Snow-Harter C, Marcus R: Exercise, bone mineral density, and osteoporosis. In: Exercise and Sport Sciences Reviews, pp 351–88. Edited by Holloszy JO. Baltimore, MD, Williams & Wilkins, 1991.
4. Wadden TA, Vogt RA, Foster GD, Anderson DA: Exercise and the maintenance of weight loss: 1-year follow-up of a controlled clinical trial. J Consult Clin Psychol 1998; 66: 429–33.
5. Fulcher K, White P: Randomized controlled trial of graded exercise in patients with the chronic fatigue syndrome. Br Med J 1997; 314: 1647–52.
6. Bennett R, Clar S, Goldber L, et al: Aerobic fitness in patients with fibrositis: a controlled study of respiratory gas exchange and ^{133}xenon clearance from exercising muscle. Arthritis Rheum 1989; 32: 454–60.

7. Martin L, Nutting A, MacIntosh B, Edworthy S, Butterwick D, Cook J: An exercise program in the treatment of fibromyalgia. J Rheumatol 1996; 23: 1050–3.
8. Wigers S, Stiles T, Vogel P: Effects of aerobic exercise versus stress management treatment in fibromyalgia: a 4.5-year prospective study. Scand J Rheumatol 1996; 25: 77–86.
9. Donta ST, Clauw DJ, Engel CC, et al: A multicenter trial of cognitive behavioral therapy and aerobic exercise for Gulf War veterans' illnesses: a VA Cooperative Study (CSP 470). JAMA 2003; 289: 1396–404.
10. Salmon P: Effects of physical exercise on anxiety, depression, and sensitivity to stress: a unifying theory. Clin Psychol Rev 2000; 21: 33–61.
11. Biddle S: Exercise and psychosocial health. Res Q Exerc Sport 1995; 66: 292–7.
12. Hassmen P, Koivula N, Uutela A: Physical exercise and psychological well-being: a population study in Finland. Prev Med 2000; 30: 17–25.
13. Hoad NA, Crawford IC: Rehabilitation after coronary artery by-pass grafting and improved quality of life. Br J Sports Med 1990; 24: 120–2.
14. Young-McCaughan S, Sexton DL: A retrospective investigation of the relationship between aerobic exercise and quality of life in women with breast cancer. Oncol Nurs Forum 1991; 18: 751–7.
15. Wankel L, Sefton J: Physical activity in other lifestyle behaviors. In: Physical Activity, Fitness, and Health Campaign, pp 530–50. Edited by Bouchard C, Shephard R, Stephens T. Champaign, IL, Human Kinetics, 1994.
16. U.S. Public Health Service: Understanding and Promoting Physical Activity: The Surgeon General's Report on Physical Activity and Health. Washington, DC, Department of Health and Human Services, 1996.
17. Jones DA, Ainsworth BE, Croft JB, Macera CA, Lloyd EE, Yusuf HR: Moderate leisure-time physical activity: who is meeting the public health recommendations? A national cross-sectional study. Arch Fam Med 1998; 7: 285–9.
18. Dishman RK: Overview. In: Exercise Adherence, pp 1–9. Edited by Dishman RK. Champaign, IL, Human Kinetics, 1988.
19. Martin JE, Dubbert PM: Adherence to exercise. Exerc Sport Sci Rev 1985; 13: 137–67.
20. Bock BC, Marcus BH, Pinto BM, Forsyth LH: Maintenance of physical activity following an individualized motivationally tailored intervention. Ann Behav Med 2001; 23: 79–87.
21. Marcus BH, Forsyth L, Stone EJ, et al: Physical activity behavior change: issues in adoption and maintenance. Health Psychol 2000; 19: 32–41.
22. Schneider SH, Khachadurian AK, Amorosa LF, Clemow L, Ruderman NB: Ten-year experience with an exercise-based outpatient life-style modification program in the treatment of diabetes mellitus. Diabetes Care 1992; 15: 1800–10.
23. Fentem PH: Benefits of exercise in health and disease. Br Med J 1994; 308: 1291–5.
24. Guarino P, Peduzzi P, Donta S, et al: A multicenter two-by-two factorial trial of cognitive behavioral therapy and aerobic exercise for Gulf War veterans' illnesses: design of a Veterans Affairs Cooperative Study (CSP 470). Controlled Clin Trials 2001; 22: 310–32.
25. Borg G: Perceived exertion as an indicator of somatic stress. Scand J Rehabil Med 1970; 2: 92–8.
26. Kazis LE, Miller DR, Clark J, et al: Health related quality of life in patients served by the Department of Veterans Affairs: results from the Veterans Health Study. Arch Intern Med 1998; 158: 626–32.
27. Kazis LE, Skinner K, Rogers W, Lee A, Ren XS, Miller D: Health Status and Outcomes of Veterans: Physical and Mental Component Summary Scores (SF-36V): 1998 National Survey of Ambulatory Care Patients: Mid-year Executive Report. Washington, DC, Veterans Administration, Health Services Research and Development Service, Office of Performance and Quality, Health Assessment Project, Center for Health Quality Outcomes and Economic Research, 1998.
28. Ware J, Sherbourne C: The MOS 36-item short-form health survey (SF-36), part I: conceptual framework and item selection. Med Care 1995; 30: 473–83.
29. Melzack R: The short-form McGill Pain Questionnaire. Pain 1987; 30: 191–7.
30. Smets EM, Garssen B, Bonke B, DeHaes JC: The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995; 39: 315–25.
31. Schluederberg A, Straus S, Peterson P, et al: Chronic fatigue syndrome research: definition and medical outcome assessment. Ann Intern Med 1992; 117: 325–31.
32. Broadbent DE, Cooper PF, FitzGerald P, Parkes KR: The Cognitive Failures Questionnaire (CF) and its correlates. Br J Clin Psychol 1981; 21: 1–16.
33. Spitzer R, Williams J, Kroenke K, et al: Utility of a new procedure for diagnosing mental disorders in primary care: the PRIME-MD 1000 study. JAMA 1994; 272: 1749–56.
34. Horowitz L, Rosenberg S, Baer B, Ureno G, Villasenor V: Inventory of Interpersonal Problems: psychometric properties and clinical applications. J Consult Clin Psychol 1988; 56: 885–92.
35. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR: A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996; 49: 1373–9.
36. U.S. Department of Health and Human Services: Healthy People 2010, Conference Ed. Washington, DC, U.S. Government Printing Office, 2000.
37. Goodall TA, Halford WK: Self-management of diabetes mellitus: a critical review. Health Psychol 1991; 10: 1–8.

Review

Biology and therapy of fibromyalgia

Functional magnetic resonance imaging findings in fibromyalgia

David A Williams[1,2] and Richard H Gracely[1,3]

[1]Chronic Pain and Fatigue Research Center, Department of Internal Medicine, Division of Rheumatology, University of Michigan Health System, University of Michigan, Ann Arbor, MI, USA
[2]Department of Psychiatry, University of Michigan Health System, University of Michigan, Ann Arbor, MI, USA
[3]Department of Neurology, University of Michigan Health System, University of Michigan and Ann Arbor VAMC, Ann Arbor, MI, USA

Corresponding author: Richard H Gracely, rgracely@med.umich.edu

Published: 17 January 2007
This article is online at http://arthritis-research.com/content/8/6/224

Arthritis Research & Therapy 2006, **8:**224 (doi:10.1186/ar2094)

Abstract

Techniques in neuroimaging such as functional magnetic resonance imaging (fMRI) have helped to provide insights into the role of supraspinal mechanisms in pain perception. This review focuses on studies that have applied fMRI in an attempt to gain a better understanding of the mechanisms involved in the processing of pain associated with fibromyalgia. This article provides an overview of the nociceptive system as it functions normally, reviews functional brain imaging methods, and integrates the existing literature utilizing fMRI to study central pain mechanisms in fibromyalgia.

Introduction

Fibromyalgia (FM) affects six to ten million Americans, [1] and the incidence is estimated to be one to four percent in the general population [2]. The symptoms associated with FM significantly affect patients' quality of life [3] and can lead to extensive use of health care services [4]. Fibromyalgia is experienced as a chronic, widespread pain condition accompanied by fatigue, tenderness, sleep disturbance, decrements in physical functioning, and disruptions in psychological functioning (for example, memory problems, diminished mental clarity, mood disturbances, and lack of well-being) [5,6]. To date, a precise cause of FM is unknown.

The diagnostic criteria for FM are, in part, based upon a demonstration of tenderness in 11 of 18 defined muscular sites [7]. Recent evidence, however, suggests the tenderness is not confined to these sites in FM, but can be observed throughout the body, including non-muscular sites such as the thumb [8]. The general and widespread nature of pain in fibromyalgia strongly suggests the involvement of central mechanisms that facilitate bodily spontaneous pain and that increase sensitivity to painful blunt pressure. These central mechanisms may involve spinal or supraspinal modulation of normal peripheral input, or efferent mechanisms that alter pain sensitivity at the periphery. These underlying central mechanisms of FM are likely to be reflected in altered supraspinal processing and may originate, in part, at supraspinal sites.

The ability to evaluate human supraspinal processing has been enhanced greatly by major advances in brain imaging techniques. These methods vary in invasiveness, and in temporal and spatial resolution. These procedures evaluate neural activity from cerebral blood flow or glucose metabolism, neurochemistry from resonance spectroscopy techniques, changes in the volume of anatomical structures, and the amount of receptor binding by specific ligands. The focus of this paper is to describe the recent use of functional brain imaging techniques in studies of FM. It begins with a description of the nociceptive system as it functions normally, follows with an overview of functional brain imaging methods, and concludes with a synopsis of functional magnetic resonance imaging (fMRI) findings, shedding light on aberrant central mechanisms responsible for the pain of FM.

The nociceptive system

The nociceptive system is a warning system of actual or imminent damage to the body. It is a self-contained sensory system composed of peripheral sensory fibers (primary afferents) connected to multiple spinal tracts and brain regions. Normally, relatively intense noxious stimuli are required to activate this system, a feature most likely associated with promoting, rather than hindering, adaptive behavior.

ACC = anterior cingulate cortex; BOLD = blood oxygen level dependent; FM = fibromyalgia; fMRI = functional magnetic resonance imaging; IC = insular cortex; PET = positron emission tomography; PFC = prefrontal cortex; rCBF = regional cerebral blood flow; SI = primary somatosensory cortex; SII = secondary somatosensory cortex; SPECT = single photon emission computed tomography.

Peripheral nociceptors

Sensory fibers modulating pain sensations innervate all body tissues in order to respond to the most compelling dangers (for example, heat, cold, mechanical pressure, chemical, and metabolic stimuli such as low pH). These sensory fibers are composed of two types: thinly myelinated Aδ fibers and unmyelinated C fibers. Aδ fibers are rapidly conducting and transmit signals that produce perceptions of relatively sharp, incapacitating pain. Aδ pain has been referred to as 'first pain', consistent with its ability to rapidly warn and motivate avoidance of tissue-damaging stimuli. In contrast, C fiber afferents conduct more slowly and tend to produce perceptions of aching or burning pain referred to as 'second pain'. Second pain is diffuse, prolonged and aversive, and is the main component of pain associated with chronic medical conditions [9].

Spinal cord secondary projections

Nociceptor afferents enter the spinal cord via the dorsal roots and terminate in lamina I, II, and V of the superficial dorsal horn. Activity in these nociceptors releases excitatory neurotransmitters at their terminals that activate secondary projection neurons. Excitatory transmitters include glutamate, which activates post-synaptic N-methyl-D-aspartate receptors, Substance P, and neurokinin A, which in turn activate post-synaptic neurokinin A receptors.

Neurons in lamina I and II respond to specific noxious stimuli within small receptive fields (for example, in muscle or joint). These second order neurons are termed 'nociceptive-specific' and are dominated by Aδ fiber input. Nociceptive neurons in lamina V respond to both noxious and non-noxious mechanical stimuli and are termed 'wide dynamic range' neurons.

Ascending pathways and brain networks

The secondary neurons originating within the dorsal horn ascend in three primary contralateral tracts projecting to the thalamus and reticular formation. The largest tract is the spinothalamic tract, providing nociceptive information to thalamic nuclei [10] as well as to the primary (SI) and secondary (SII) somatosensory cortices. SI and SII are cortical regions believed to be involved in sensory-discriminative aspects of pain as well as in the anticipation of painful stimuli [11]. Spinothalamic tract projections also facilitate nociceptive input to the insular cortex (IC), which has interconnections with the amygdala, prefrontal cortex (PFC), and anterior cingulate cortex (ACC). These regions form a network involved in affective, cognitive, and autonomic responses to nociception. Two of these regions (IC and PFC cortices) may also integrate nociceptive signals with memory of previous events, thus providing meaning and the identification of potential threats associated with painful stimuli [12,13]. In addition to the spinothalamic tract, there are at least two other prominent ascending pathways from the spinal cord to the brain [14-17]. Like aspects of the spinothalamic tract, both of these pathways are thought to mediate the interactions between nociceptive signals, cognition, and emotional responses.

Consistent with the above, a meta-analytic review of acute pain neuroimaging studies suggested that the six most commonly activated brain regions for pain in healthy subjects were SI, SII, IC, ACC, PFC and thalamus [18]. Interestingly, simply the anticipation of pain activates similar regions (PFC, anterior insula, ACC). These regions are involved in the formation of cognitive and affective representations of pain involving memories of past events and understandings of the present and future implications of events signaled by pain [19]. Chronic pain states on the other hand have been more difficult to study; but summary impressions suggest that relative to acute pain processing, chronic pain processing reflects decreased sensory processing (for example, SI, SII) in favor of enhanced activation of regions associated with cognitive, emotional, and introspective processing of events [18].

Neuroimaging: a summary of methods

Several neuroimaging methodologies exist, each providing a slightly different temporal window for understanding the central processing of pain. The assessment of temporal characteristics is best performed through the use of the electroencephalogram or with the more advanced application of magnetoencephalography, which offers the ability to record the timing of brain events on the order of milliseconds. These methods are best used with stimuli having temporally precise onsets, such as provided by electrical, laser and acoustic sources, or by well controlled mechanical stimulation. These methods have not been very useful for stimuli that do not have such characteristics, such as the blunt pressure used in the assessment of tenderness in FM. While good for assessing temporal characteristics, the spatial resolution of these methods is relatively poor in comparison to other methods and is aided by the use of the modalities described below.

Assessment of spatial characteristics often uses methods that do not measure neural activity directly but, instead, use specialized equipment to infer neural activity from highly localized increases in regional cerebral blood flow (rCBF) occurring in response to anticipated neural metabolic demand. The local increase in rCBF can be imaged by infusion of radioactive tracers with methods such as single photon emission computed tomography (SPECT) or positron emission tomography (PET). In the case of fMRI, the different magnetic properties of oxygenated and deoxygenated blood serve as an intrinsic tracer (that is, the blood oxygen level dependent (BOLD) fMRI signal).

The various imaging methods differ in the ability to assess baseline rCBF, and in temporal and spatial resolution. One advantage of the early methods of SPECT and PET is that they could assess static rCBF; for example, comparing the

baseline neural activity among different patient populations. Relative disadvantages were the need to infuse radioactive tracers, and modest temporal and spatial resolution. The time needed for a single image of the entire brain was approximately 30 minutes with SPECT, 1 minute with PET, and 2 seconds with fMRI. Localization also improves accordingly; fMRI methods now allow visualization of activity in discrete regions, such as thalamic nuclei, with resolutions as small as 1 to 2 mm. A potential disadvantage of the fMRI BOLD, however, is that such designs must repeatedly switch between stimulus 'on' and 'off' conditions, making imaging of static or long-lasting drug effects (for example, before and after treatment) more difficult.

Evaluation of pain processing in fibromyalgia

Early SPECT studies

The pioneering application of brain functional imaging to patients with FM used the SPECT method. Mountz [20] used SPECT to evaluate baseline levels of rCBF in ten patients with fibromyalgia and in seven healthy control subjects. In this initial study, patients received infusions of approximately 25 mCi of ^{99m}Tc-HMPAO, a radioactive tracer that facilitated the imaging of rCBF. After the infusion, the subjects underwent a 32 minute SPECT scan. This method resulted in a semi-quantitative measure of rCBF with a resolution of about 8.5 mm. The analysis examined overall activity in large regions of interest corresponding to the right and left thalamus and the right and left head of the caudate nucleus. Results from this early study suggested that patients with FM had lower rCBF (that is, lower neural activity) than healthy control subjects during a quiescent resting state. Reduced neural activity was found both in the right and left thalamus and in the right and left caudate nucleus.

Another group followed this initial investigation with a similar study. Kwiatek [21] used SPECT to assess resting rCBF in 17 patients with FM and in 22 healthy control subjects. These investigators observed decreased rCBF in the right thalamus, the inferior pontine tegementum and near the right lentiform nucleus but, unlike the initial study, no decreases in either the left thalamus or in the caudate nuclei were noted.

The consistent finding of reduced rCBF in the right thalamus was also observed in a second study by the Mountz group [22], who examined the influence of historical factors on the SPECT results. These authors divided the sample of patients with fibromyalgia into those with a traumatic etiology ($n = 11$) and those with a more gradual onset ($n = 21$). Both patient groups, compared to 29 healthy controls, showed significantly decreased rCBF in the left and right thalamus. However, only patients with a gradual atraumatic etiology showed reduced rCBF in the left and right caudate.

The findings of decreased rCBF in the thalamus and in the caudate nucleus are not unique to FM. Low rCBF has been observed in patients with pain due to traumatic peripheral neuropathy [23] and to metastatic breast cancer [24]. Abnormally low rCBF levels in the caudate nucleus have been documented in patients with pain related to spinal cord injury [25], and in restless leg syndrome [26]. The caudate nucleus receives a large nociceptive input from spinal pain pathways, including both nociceptive-specific neurons that signal the presence of pain, and wide-dynamic-range neurons that provide graded responses throughout the range of innocuous and painful stimulation [27-29].

The caudate nucleus may also be involved in intrinsic analgesia systems [30,31]. Although the cause of thalamic and caudate decreases in rCBF is unknown, inhibition of activity in these regions is associated with, and may result from, prolonged excitatory nociceptive input [23]. The present findings of lowered resting rCBF in these structures in FM patients are consistent with a mechanism of tonic inhibition maintained by persistent excitatory input associated with ongoing and spontaneous pain. That is, the widespread pain in FM is sufficient to activate pain inhibitory mechanisms, and one consequence of this inhibition is reduced resting and evoked activity in the thalamus.

Methodological considerations for using the improved spatial resolution of fMRI

Before fMRI could be used to explore underlying pain mechanisms in FM, several methodological hurdles needed to be resolved. Unlike acute or surgical pain, where the nature and timing of the pain stimulus can be controlled, imaging FM pain is more challenging given that neither the experimenter nor the patient has the ability to systematically manipulate the characteristics of the condition [18]. Thus, methodological advances for delivering and removing a standardized pain stimulus needed to be made that would permit: the rapid onset and off-set of the evoked-pain stimuli; the delivery of stimuli that were relatively unbiased by psychosocial factors; and the use of a pain stimulus that was meaningful and relevant to the condition of FM.

Many studies of FM pain apply pressure to specific FM tender points. This is commonly done using 'ascending' testing methods, such as tender point counts or dolorimetry, where each subsequent stimulus is predictable in its intensity. These methods are easy to apply clinically, but can be influenced by response biases originating from both the subject and examiner. Improved methods that present stimuli in a random, unpredictable fashion (for example, Multiple Random Staircase) tend to minimize the influence of these factors [32].

fMRI studies have the added methodological hurdle of needing to apply standardized pressure to regions of the body accessible during scanning and with methods that can be accommodated within the scanning environment. Thus, methods were devised that applied blunt pressure (1 cm diameter hard rubber probe) to the thumbnail. This site was

chosen for the dense innervation of the thumb, and the large representation of the thumb in the primary somatosensory cortex. In addition, this site implicitly acknowledges that the tenderness observed in FM is not confined to classic tender points; tenderpoints, rather, are regions in which everyone is more tender and are thus more convenient for manual testing. The use of the thumb also implicitly implies that the tenderness observed in FM is neither due to muscle sensitivity nor confined to muscles but, rather, is a property of deep tissue, with the tenderness of FM being generally expressed over the entire body.

Another extremely important methodological consideration addressed the fact that patients and controls differed not only with respect to the presence of clinical pain but also to the fact that the presence of concomitant clinical pain could alter their perception of the evoked pain stimuli. Thus, responses to stimuli needed to be evaluated in the context of equal stimulus intensities for patients and controls and under conditions of equal perceptual intensities. This approach permitted comparisons of neural activations between FM patients and normal controls associated with pain processing when either perceived pain intensity or stimulus intensities were constant.

Central pain augmentation in fibromyalgia

Using pressure-based Multiple Random Staircase to equate evoked pain perception between patients and normal controls, one of the first fMRI studies of FM applied blunt pressure to the left thumbnail bed of 16 right-handed patients with FM and 16 right-handed matched controls [33]. Each FM patient underwent fMRI while moderately painful pressure was being applied. The functional activation patterns in FM patients were compared with patterns in normal controls. The results show that equal perceived pain intensity (achieved with significantly less pressure in the patients than controls), produced similar increases in neural activity in a network of brain structures implicated in pain processing (Figure 1). These increases were observed in structures involved in sensory discriminative processing (contralateral SI, SII), sensory association (contralateral superior temporal gyrus, inferior parietal lobule), motor responses (contralateral putamen and ipsilateral cerebellum) and affective processing (contralateral insula). Patients and controls also shared a similar region of decreased neural activation in the ipsilateral SI.

In contrast to the extensive common activations observed in both patients and controls when subjective pain perception was equated, there were no common activations when the actual pressure stimulus intensity was equated. Applying a low stimulus pressure to both healthy controls and FM patients resulted in 13 regions showing statistically greater activation for patients (that is, contralateral SI, inferior parietal lobule, insula, ACC and posterior cingulate cortex; ipsilateral SII cortex; bilateral superior temporal gyrus, and cerebellum) whereas only one region (ipsilateral medial frontal gyrus) demonstrated greater activation in controls.

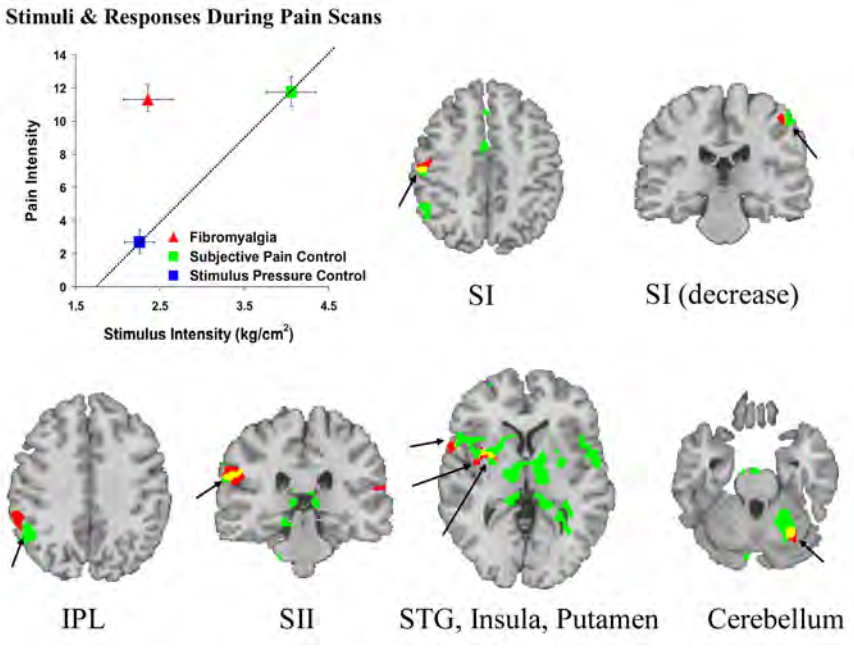
These findings suggest that the greater perceived intensity of standardized low pressure stimuli by persons with FM is consistent with a model of centrally augmented pain processing. These results also suggest that the brain activations in patients and controls are consistent with their verbal reports of pain magnitude. In addition, these results demonstrate that, in the caudate nucleus and the thalamus, patients with FM showed reduced activation in comparison to controls. This lack of response is, at first glance, consistent with the finding of reduced basal activity in these structures [20-22]. However, it is important to note that the finding of basal levels could indicate either lack of evoked pain responsivity (inhibited system) or be responsible for increased pain sensitivity (greater response range; that is, activity can increase further before encountering a physiological 'ceiling'). Thus, this apparently consistent result is not necessarily expected and the implications of these results will depend on the results of further studies [33].

The findings of the Gracely and colleagues [33] study have been supported by a second study using a contact heat stimulus. Cook and colleagues [34] showed that perceptually matched heat pain stimuli (that is, matched subjective perceptual pain ratings) applied to the left hand (evoked by less heat in patients (mean 47.4°C) versus controls (48.3°C)) resulted in similar brain activation patterns between a group of 9 female FM patients and 9 female healthy controls. In contrast, when evoked-pain stimuli were matched on actual stimulus intensity (that is, temperature), significantly greater activations in contralateral IC were seen in FM patients. In addition, these authors compared responses to non-painful heat stimuli, and observed that random warm stimuli between 34°C and 42°C evoked significantly greater activity in FM patients in bilateral PFC, supplemental motor areas, and in contralateral ACC.

Mechanisms of hyperalgesia in fibromyalgia

Hyperalgesia refers to a condition where normally noxious stimuli produce an exaggerated or prolonged pain response. In an attempt to image a hyperalgesic response to evoked pain, Grant and colleagues [35] used fMRI to compare the effects of multiple stimulus pressures delivered to the left thumb of 13 FM patients and 13 control subjects. During scanning, the subjects received 25 seconds of no pressure alternating with 25 seconds of pressure stimuli adjusted for each subject to produce: a non-painful touch sensation; painful pressure sensations rated as 'faint'; sensations rated as 'very mild'; and sensations rated between 'moderate' and 'slightly intense' pain. In each scan the subjects received each of the four stimulus pressures three times in a random sequence. Similar to the study described above [33], the amount of stimulus pressure needed to evoke the various subjective levels of pain was significantly lower in the patients; however, both patients and controls showed graded responses to stimulus pressure in regions involved in processing the sensory discriminative dimension of pain

Figure 1



Functional magnetic resonance imaging (fMRI) responses to painful pressure applied to the left thumb in patients with fibromyalgia and healthy control subjects. The top left graph shows mean pain rating plotted against stimulus intensity for the experimental conditions. In the 'patient' condition, a relatively low stimulus pressure (2.4 kg/cm^2) produced a high pain level (11.30 ± 0.90), shown by the red triangle. In the 'stimulus pressure control' condition, shown by the blue square, administration of a similar stimulus pressure (2.33 kg/cm^2) to control subjects produced a very low level of rated pain (3.05 ± 0.85). In the 'subjective pain control' condition, shown by the green square, administration of significantly greater stimulus pressures to the control subjects (4.16 kg/cm^2) produced levels of pain (11.95 ± 0.94) similar to the levels produced in patients by lower stimulus pressures. The remainder of the figure shows common regions of activation in patients (red) and in the 'subjective pain control' condition (green), in which the effects of pressure applied to the left thumb sufficient to evoke a pain rating of 11 (moderate) is compared to the effects of innocuous pressure. Significant increases in the fMRI signal resulting from increases in regional cerebral blood flow are shown in standard space superimposed on an anatomical image of a standard brain (MEDx, Medical Numerics, Inc. 20410 Observation Drive, Suite 210, Germantown, Maryland 20876 USA). Images are shown in radiological view with the right brain shown on the left. Overlapping activations are shown by yellow. The similar pain intensities, produced by significantly less pressure in the patients, resulted in overlapping or adjacent activations in contralateral primary somatosensory cortex (SI), inferior parietal lobule (IPL), secondary somatosensory cortex (SII), superior temporal gyrus (STG), insula, putamen, and in ipsilateral cerebellum. The fMRI signal was significantly decreased in a common region in ipsilateral SI. Modified from Gracely and colleagues [33].

sensation, including contralateral (right) thalamus, SI and SII. Control subjects showed graded responses in right insula and anterior cingulate that were not found in the patients. These results indicate common sensory discriminative functions in both groups that occur with lower objective stimulus intensities for FM patients. The reduced affective response (that is, no activation in ACC or insula in FM patients) suggests that FM patients may not find the evoked pain stimulus affectively arousing due, possibly, to affective adaptation associated with their prolonged pain.

Affective modulation of pain in fibromyalgia

Depressed mood often accompanies chronic pain, but depressed mood may not augment the sensory aspects of pain. Instead, mood may exert its own independent influence on pain processing. Giesecke and colleagues [36] conducted a study that evaluated the effect of symptoms of depression and/or clinically diagnosed major depressive disorder on pain processing in patients with FM. In this study, 30 patients with FM received fMRI scans during administration of painful blunt pressure to the left hand matched for equally perceived painful pressure. Symptoms of depression were measured with the Center for Epidemiological Studies Depression Scale (CES-D). Neither the extent of depression nor the presence of comorbid major depression modulated the sensory-discriminative aspects of pain processing (that is, localized imaging of sensory pain and reporting its level of intensity). However, symptoms of depression and the presence of major depressive disorder were associated with the magnitude of evoked-pain neuronal activations in brain regions associated with affective-motivational pain processing (that is, the bilateral amygdalae and contralateral anterior insula). These data suggest that there are parallel, somewhat independent neural pain-processing networks for sensory and affective pain elements. The implication for treatment is that addressing an individual's depression (for example, by

prescribing an antidepressant medication that has no analgesic properties) will not necessarily have an impact on the sensory dimension of pain.

Cognitive modulation of pain in fibromyalgia

Locus of control

Locus of control for pain refers to patients' perceptions about their personal ability to control pain. In studies of patients with chronic rheumatological pain conditions, a stronger belief in internal locus of control for pain has been associated with lower levels of physical and psychological symptoms, and better response to therapy [37-45]. In studies of patients with FM, internal locus of control has been associated with better affect, reduced symptom severity, and less disability in upper and lower extremity function [46] and generally improved levels of functional status [47]. Most patients with FM, however, are more external in their locus of control compared to other rheumatological conditions or patients with chronic pain generally [46,48,49]. Several of these studies have concluded that increasing internal locus of control in patients with FM should increase the likelihood of improving function and decreasing impairment (for example, McCarberg and colleagues [47]). In a study designed to explore the neural substrates of locus of control, a sample of 20 females and 1 male meeting American College of Rheumatology criteria for FM were selected [50]. Each patient received fMRI scans during administration of painful blunt pressure to the left hand matched for equally perceived painful pressure. Locus of pain control was assessed using the Beliefs in Pain Control Questionnaire [51]. Results of this study found that stronger beliefs in an internal locus of control were significantly correlated with neuronal activations in the contralateral SII ($r = 0.84$, $p < 0.05$) in response to evoked pain. These results support the hypothesis that greater levels of internal locus of control are associated with greater magnitude of neuronal activation in this region associated with sensory discrimination and pain intensity encoding.

Catastrophizing

Another common cognitive factor known to modulate pain reports is catastrophizing, an attributional style/behavior in which pain is characterized as awful, horrible and unbearable. Catastrophizing appears to play a substantial role in the development of pain chronicity. Burton and colleagues [52] found that catastrophizing accounted for over half (57%) of the variance in predicting the onset of a chronic pain condition from an acute pain event. Catastrophizing was once thought to be a symptom of depression but is now recognized as an independent factor that is only partially associated with depression. Catastrophizing has been suggested to augment pain perception via enhanced attention to painful stimuli and through heightened emotional responses to pain. This study hypothesized that catastrophizing would, therefore, influence activation of neural structures implicated in pain processing. Blunt pressure pain was applied to 29 FM patients while controlling for depression statistically. Independent of depression, catastrophizing modulated evoked-pain activity in a number of brain structures related to the anticipation of pain (contralateral medial frontal cortex, ipsilateral cerebellum), attention to pain (contralateral anterior cingulate gyrus, bilateral dorsolateral prefrontal cortex), and to both emotional (ipsilateral claustrum, interconnected to the amygdala) and motor (contralateral lentiform nuclei) responses [53]. These findings suggest that pain catastrophizing exerts influence on pain processing that is independent of the influence of depression and supports the hypothesis that catastrophizing influences pain perception through altering attention and anticipation, and heightening emotional responses to pain. Like locus of control, therapies targeting the modification of catastrophizing might be useful in preventing the transition from acute to chronic pain in susceptible individuals.

Fibro-fog

While cognition appears to modulate the experience of pain, it is also likely that pain interferes with the ability to think and process information. A well-known complaint of patients with FM is that of an overall impaired cognitive state that has been referred to as 'fibro fog'.

The cognitive deficits observed in FM resemble those found in aging. For example, patients with FM tend to complete measures of working memory with a proficiency that is similar to healthy controls who are 20 years older [54,55]. Neuroimaging studies of working memory in aged populations suggest that older subjects can show levels of performance that approach the levels of younger control subjects but must use relatively more cognitive resources. Bangert and colleagues [55] used fMRI to assess brain activity during a working memory task in 12 FM patients and 9 age and education-matched control subjects. The results show that both FM patients and healthy controls were able to achieve similar performances on the tasks. The imaging results, however, revealed that, in order to achieve this similar level of performance, FM patients needed to use far greater brain resources. FM patients showed more extensive neural activation in frontal and parietal regions, including bilateral activation in the middle frontal gyrus and right-side activation in medial frontal gyrus, superior parietal lobe, and precentral gyrus. These results support the hypothesis that FM patients show an aging effect that is using increasing cognitive resources to maintain comparable levels of performance as their same-aged peers.

Conclusions and future directions

At the present time, functional brain imaging in FM has revealed the following insights. First, FM patients differ from healthy controls in baseline levels of neural activity, specifically in the caudate nucleus. Second, administration of a noxious pressure or heat stimulus results in changes in brain activity consistent with the verbal reports of patients' pain intensity. Third, like healthy controls, FM patients normally detect and experience a full range of perceived pain

magnitude; but sensations become unpleasant at stimulus intensities that are significantly lower than those observed in healthy controls. Fourth, while commonly associated with chronic pain, depression does not appear to influence the sensory-discriminative dimension of pain in FM. Fifth, attitudes and beliefs such as locus of control and catastrophizing appear to be influential in the processing of sensory-discriminative aspects of pain. Sixth, FM patients utilize more extensive brain resources than do same-aged peers in order to achieve comparable performance on cognitive tasks.

Limitations and future potential of fMRI in fibromyalgia

Currently, most fMRI activation studies can only assess the effects of short interventions that can be turned 'on' and 'off' repeatedly within seconds to a minute. Thus, conventional fMRI cannot directly assess the effect of an oral analgesic on the clinical pain of FM but can assess the interaction of the analgesic with a repeated brief stimulus such as painful heat or pressure. Newer MRI methodologies are changing this limitation and expanding the types of physiological variables that can be evaluated by functional brain imaging. Magnetic resonance perfusion can assess cerebral blood flow and cerebral blood volume, providing measures of baseline differences similar to that currently provided by PET. Diffusion tensor imaging, another variant of fMRI, provides a non-invasive, *in vivo* assessment of water molecular diffusion that reflects tissue configuration at a microscopic level in white matter regions. Quantification of water diffusion will improve the neuro-radiological assessment of a variety of gray and white matter disorders, including those involved in pain processing. Yet another new approach, magnetic resonance spectroscopy, obtains spectra of multiple selected regions and determines the ratio of concentrations of metabolites such as N-acetyl-aspartate, creatine, choline, lactate, glucose and glutamate. Usually, a particular stable metabolite (for example, creatine) is used as a standard and the concentration of the test metabolites are expressed as a ratio to this standard. Abnormalities in the levels of these metabolites are associated with a number of pathological changes in brain tissue. This method has been applied to patients with chronic low back pain, showing reductions of N-acetyl-aspartate and glucose in dorsolateral prefrontal cortex compared to control subjects [56].

These recent applications of functional neuroimaging have provided evidence for a centralized pain augmentation in FM and identified brain regions that may be involved in this augmentation. Advances in design and new imaging technologies promise to further increase our understanding of the mechanisms that initiate and maintain this disorder, and can lead to improved diagnosis and treatment.

This review is part of a series on
Biology and therapy of fibromyalgia
edited by Leslie Crofford.

Other articles in this series can be found at
http://arthritis-research.com/articles/
review-series.asp?series=ar_fibromyalgia

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

Preparation of the manuscript was supported in part by Department of Army grant DAMD17-00-2-0018.

References

1. Goldenberg DL: **Office management of fibromyalgia.** *Rheum Dis Clin North Am* 2002, **28:**437-446, xi.
2. Brecher LS, Cymet TC: **A practical approach to fibromyalgia.** *J Am Osteopath Assoc* 2001, **101:**S12-S17.
3. Sprott H: **What can rehabilitation interventions achieve in patients with primary fibromyalgia?** *Curr Opin Rheumatol* 2003, **15:**145-150.
4. Penrod JR, Bernatsky S, Adam V, Baron M, Dayan N, Dobkin PL: **Health services costs and their determinants in women with fibromyalgia.** *J Rheumatol* 2004, **31:**1391-1398.
5. Forseth KO, Gran JT: **Management of fibromyalgia: what are the best treatment choices?** *Drugs* 2002, **62:**577-592.
6. Wolfe F, Anderson J, Harkness D, Bennett RM, Caro XJ, Goldenberg DL, Russell IJ, Yunus MB: **A prospective, longitudinal, multicenter study of service utilization and costs in fibromyalgia.** *Arthritis Rheum* 1997, **40:**1560-1570.
7. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P: **The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee.** *Arthritis Rheum* 1990, **33:**160-172.
8. Petzke F, Clauw DJ, Ambrose K, Khine A, Gracely RH: **Increased pain sensitivity in fibromyalgia: effects of stimulus type and mode of presentation.** *Pain* 2003, **105:**403-413.
9. Price DD, Hu J, Dubner R, Gracely RH: **Peripheral suppression of first pain and central summation of second pain evoked by noxious heat pulses.** *Pain* 1977, **3:5**7-68.
10. Jones AK: **The contribution of functional imaging techniques to our understanding of rheumatic pain.** *Rheum Dis Clin North Am* 1999, **25:**123-152.
11. Sawamoto N, Honda M, Okada T, Hanakawa T, Kanda M, Fukuyama H, Konishi J, Shibasaki H: **Expectation of pain enhances responses to nonpainful somatosensory stimulation in the anterior cingulate cortex and parietal operculum/posterior insula: an event-related functional magnetic resonance imaging study.** *J Neurosci* 2000, **20:**7438-7445.
12. Treede RD, Kenshalo DR, Gracely RH, Jones AK: **The cortical representation of pain.** *Pain* 1999, **79:**105-111.
13. Coghill RC, Sang CN, Maisog JM, Iadarola MJ: **Pain intensity processing within the human brain: A bilateral, distributed mechanism.** *J Neurophysiol* 1999, **82:**1934-1943.
14. Rainville P: **Brain mechanisms of pain affect and pain modulation.** *Curr Opin Neurobiol* 2002, **12:**195-204.
15. Koyama T, Kato K, Mikami A: **During pain-avoidance neurons activated in the macaque anterior cingulate and caudate.** *Neurosci Lett* 2000, **283:**17-20.
16. Desbois C, Villanueva L: **The organization of lateral ventromedial thalamic connections in the rat: a link for the distribution of nociceptive signals to widespread cortical regions.** *Neuroscience* 2001, **102:**885-898.
17. Bourgeais L, Gauriau C, Bernard JF: **Projections from the nociceptive area of the central nucleus of the amygdala to the forebrain: a PHA-L study in the rat.** *Eur J Neurosci* 2001, **14:** 229-255.
18. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK: **Human brain mechanisms of pain perception and regulation in health and disease.** *Eur J Pain* 2005, **9:**463-484.
19. Koyama T, McHaffie JG, Laurienti PJ, Coghill RC: **The subjective experience of pain: where expectations become reality.** *Proc Natl Acad Sci USA* 2005, **102:**12950-12955.

20. Mountz JM, Bradley LA, Modell JG, Alexander RW, Triana-Alexander M, Aaron LA, Stewart KE, Alarcon GS, Mountz JD: **Fibromyalgia in women. Abnormalities of regional cerebral blood flow in the thalamus and the caudate nucleus are associated with low pain threshold levels.** *Arthritis Rheum* 1995, **38:**926-938.
21. Kwiatek R, Barnden L, Tedman R, Jarrett R, Chew J, Rowe C, Pile K: **Regional cerebral blood flow in fibromyalgia: single-photon-emission computed tomography evidence of reduction in the pontine tegmentum and thalami.** *Arthritis Rheum* 2000, **43:**2823-2833.
22. Bradley LA, Sotolongo A, Alberts KR, Alarcon GS, Mountz JM, Liu HG, Kersh BC, Domino ML, De Waal D, Weigent DA, Blalock JE: **Abnormal regional cerebral blood flow in the caudate nucleus among fibromyalgia patients and non-patients is associated with insidious symptom onset.** *J Musculoskeletal Pain* 1999, **7:** 285-292.
23. Iadarola MJ, Max MB, Berman KF, Byas-Smith MG, Coghill RC, Gracely RH, Bennett GJ: **Unilateral decrease in thalamic activity observed with positron emission tomography in patients with chronic neuropathic pain.** *Pain* 1995, **63:**55-64.
24. Di Piero V, Jones AK, Iannotti F, Powell M, Perani D, Lenzi GL, Frackowiak RS: **Chronic pain: A PET study of the central effects of percutaneous high cervical cordotomy.** *Pain* 1991, **46:**9-12.
25. Ness TJ, San Pedro EC, Richards JS, Kezar L, Liu HG, Mountz JM: **A case of spinal cord injury-related pain with baseline rCBF brain SPECT imaging and beneficial response to gabapentin.** *Pain* 1998, **78:**139-143.
26. San Pedro EC, Mountz JM, Mountz JD, Liu HG, Katholi CR, Deutsch G: **Familial painful restless legs syndrome correlates with pain dependent variation of blood flow to the caudate, thalamus, and anterior cingulate gyrus.** *J Rheumatol* 1998, **25:** 2270-2275.
27. Sorkin LS, McAdoo DJ, Willis WD: **Stimulation in the ventral posterior lateral nucleus of the primate thalamus leads to release of serotonin in the lumbar spinal cord.** *Brain Res* 1992, **581:**307-310.
28. Chudler EH, Sugiyama K, Dong WK: **Nociceptive responses in the neostriatum and globus pallidus of the anesthetized rat.** *J Neurophysiol* 1993, **69:**1890-1903.
29. Diorio D, Viau V, Meaney MJ: **The role of the medial prefrontal cortex (cingulate gyrus) in the regulation of hypothalamic-pituitary-adrenal responses to stress.** *J Neurosci* 1993, **13:** 3839-3847.
30. Lineberry CG, Vierck CJ: **Attenuation of pain reactivity by caudate nucleus stimulation in monkeys.** *Brain Res* 1975, **98:** 119-134.
31. Acupuncture Anesthesia Coordinating Group: **Observations on electrical stimulation of the caudate nucleus of human brain and acupuncture in treatment of intractable pain.** *Chin Med J (Engl)* 1977, **3:**117-124.
32. Gracely RH, Lota L, Walter DJ, Dubner R: **A multiple random staircase method of psychophysical pain assessment.** *Pain* 1988, **32:**55-63.
33. Gracely RH, Petzke F, Wolf JM, Clauw DJ: **Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia.** *Arthritis Rheum* 2002, **46:**1333-1343.
34. Cook DB, Lange G, Ciccone DS, Liu WC, Steffener J, Natelson BH: **Functional imaging of pain in patients with primary fibromyalgia.** *J Rheumatol* 2004, **31:**364-378.
35. Grant MA, Farrell MJ, Kumar R, Clauw DJ, Gracely RH: **fMRI evaluation of pain intensity coding in fibromyalgia patients and controls [abstract].** *Arthritis Rheum* 2001, **44:**S394.
36. Giesecke T, Gracely R H, Williams DA, Geisser M, Petzke F, Clauw DJ: **The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort.** *Arthritis Rheum* 2005, **52:**1577-1584.
37. Crisson JE, Keefe FJ: **The relationship of locus of control to pain coping strategies and psychological distress in chronic pain patients.** *Pain* 1988, **35:**147-154.
38. Rudy TE, Kerns RD, Turk DC: **Chronic pain and depression: toward a cognitive-behavioral mediation model.** *Pain* 1988, **35:**129-140.
39. Jensen MP, Turner JA, Romano JM, Karoly P: **Coping with chronic pain: A critical review of the literature.** *Pain* 1991, **47:** 249-283.
40. Strong J, Ashton R, Cramond T, Chant D: **Pain intensity, attitude and function in back pain patients.** *Aus Occupational Therapy J* 1990, **37:**179-183.
41. Gibson SJ, Helme RD: **Cognitive factors and the experience of pain and suffering in older persons.** *Pain* 2000, **85:**375-383.
42. Lipchik GL, Milles K, Covington EC: **The effects of multidisciplinary pain management treatment on locus of control and pain beliefs in chronic non-terminal pain.** *Clin J Pain* 1993, **9:**49-57.
43. Hagglund KJ, Haley WE, Reveille JD, Alarcon GS: **Predicting individual diffrences in pain and functional impairment amoung patients with rheumatoid arthritis.** *Arthritis Rheum* 1989, **32:**851-858.
44. Flor H, Turk DC: **Chronic back pain and rheumatoid arthritis: predicting pain and disability from cognitive variables.** *J Behav Med* 1988, **11:**251-265.
45. Parker JC, Frank RG, Beck NC, Smarr KL, Buescher KL, Phillips LR, Smith EI, Anderson SK, Walker SE: **Pain management in rheumatoid arthritis patients. A cognitive-behavioral approach.** *Arthritis Rheum* 1988, **31:**593-601.
46. Pastor MA, Salas E, Lopez S, Rodriguez J, Sanchez S, Pascual E: **Patients' beliefs about their lack of pain control in primary fibromyalgia syndrome.** *Br J Rheumatol* 1993, **32:**484-489.
47. McCarberg B, Wolf J, Oliver K, Fakhry F, Walen H, Cronan T: **The relationship between health locus of control and well-being in fibromyalgia patients.** *Jof Pain* 2002, **3:**14.
48. Burckhardt CS, Bjelle A: **Perceived control: A comparison of women with fibromyalgia, rheumatoid arthritis, and systemic lupus erythematosus using a Swedish version of the Rheumatology Attitudes Index.** *Scand J Rheumatol* 1996, **25:** 300-306.
49. Gustafsson M, Gaston-Johansson F: **Pain intensity and health locus of control: A comparison of patients with fibromyalgia syndrome and rheumatoid arthritis.** *Patient Educ Couns* 1996, **29:**179-188.
50. Farrell MJ, VanMeter JW, Petzke F, Wolfe JM, Grant MAB, Clauw DJ, Gracely RH: **Supraspinal activity associated with painful pressure in fibromyalgia is associated with beliefs about locus of pain control [abstract].** *Arthritis Rheum* 2001, **44:**S394.
51. Skevington SM: **A standardized scale to measure beliefs about controlling pain (BPCQ): A preliminary study.** *Psychol Health* 1990, **4:**221-232.
52. Burton AK, Tillotson KM, Main CJ, Hollis S: **Psychosocial predictors of outcome in acute and subchronic low back trouble.** *Spine* 1995, **20:**722-728.
53. Gracely RH, Geisser ME, Giesecke T, Grant MA, Petzke F, Williams DA, Clauw DJ: **Pain catastrophizing and neural responses to pain among persons with fibromyalgia.** *Brain* 2004, **127:**835-843.
54. Park DC, Glass JM, Minear M, Crofford LJ: **Cognitive function in fibromyalgia patients.** *Arthritis Rheum* 2001, **44:**2125-2133.
55. Bangert AS, Glass JM, Welsh RC, Crofford LJ, Taylor SF, Park DC: **Functional magnetic resonance imaging of working memory in fibromyalgia [abstract].** *Arthritis Rheum* 2003, **48:** S90.
56. Grachev ID, Fredrickson BE, Apkarian AV: **Brain chemistry reflects dual states of pain and anxiety in chronic low back pain.** *J Neural Transm* 2002, **109:**1309-1334.

Journal Articles – 2007

Banzett RB, Gracely RH, Lansing RW. When it's hard to breathe, maybe pain doesn't matter. Focus on "Dyspnea as a noxious sensation: inspiratory threshold loading may trigger diffuse noxious inhibitory controls in humans". J Neurophysiol. 2007 Feb;97(2):959-60.

Boyd AD, Hosner C, Hunscher DA, Athey BD, Clauw DJ, Green LA. An 'Honest Broker' mechanism to maintain privacy for patient care and academic medical research. Int J Med Inform. 2007 May-Jun;76(5-6):407-11.

Csako G, Costello R, Shamim EA, O'hanlon TP, Tran A, Clauw DJ, Williams HJ, Miller FW. Serum proteins and paraproteins in women with silicone implants and connective tissue disease: a case-control study. Arthritis Res Ther. 2007 Sep 17;9(5):R95 [Epub ahead of print]

Geisser ME, Gracely RH, Giesecke T, Petzke FW, Williams DA, Clauw DJ. The association between experimental and clinical pain measures among persons with fibromyalgia and chronic fatigue syndrome. Eur J Pain. 2007 Feb;11(2):202-7.

Gracely RH, Undem BJ, Banzett RB. Cough, pain and dyspnoea: Similarities and differences. Pulm Pharmacol Ther. 2007;20:433-437. Epub 2007 Jan 10

Harris RE, Clauw DJ, Scott DJ, McLean SA, Gracely RH, and Zubieta J-K. Decreased Central μ-Opioid Receptor (MOR) Availability in Fibromyalgia (FM). J Neuroscience. 2007 Sept;27(37):10000-10006.

Mease P, Arnold LM, Bennett R, Boonen A, Buskila D, Carville S, Chappell A, Choy E, Clauw D, Dadabhoy D, Gendreau M, Goldenberg D, Littlejohn G, Martin S, Perera P, Russell IJ, Simon L, Spaeth M, Williams D, Crofford L. Fibromyalgia syndrome. J Rheumatol 2007;34(6):1415-25.

Sundgren PC, Petrou M, Harris RE, Fan X, Foerster B, Mehrotra N, Sen A, Clauw DJ, Welsh RC. Diffusion-weighted and diffusion tensor imaging in fibromyalgia patients: a prospective study of whole brain diffusivity, apparent diffusion coefficient, and fraction anisotropy in different regions of the brain and correlation with symptom severity. Acad Radiol. 2007 Jul;14(7):839-46

Williams DA, Park KM, Ambrose KR, Clauw DJ. Assessor status influences pain recall. J Pain. 2007 Apr;8(4):343-8. Epub 2007 Jan 16.

Manuscripts Submitted for Review – 2007

Harris RE, Sundgren PC, Pang Y, Hsu M, Petrou M, Kim SH, McLean SA, Gracely RH, Clauw DJ. Dynamic Levels of Glutamate within the Insula are Associated with Improvements in Multiple Pain Domains in Fibromyalgia (FM). Arthritis Rheum, 2007, *accepted with revisions.*

J Neurophysiol 97: 959–960, 2007.
First published October 18, 2006; doi:10.1152/jn.00970.2006.

When It's Hard To Breathe, Maybe Pain Doesn't Matter. Focus on "Dyspnea as a Noxious Sensation: Inspiratory Threshold Loading May Trigger Diffuse Noxious Inhibitory Controls in Humans"

Robert B. Banzett,[1,2,3] Richard H. Gracely,[4] and Robert W. Lansing[3]

[1]*Department of Medicine, Harvard Medical School;* [2]*Division of Pulmonary and Critical Care, Beth Israel Deaconess Medical Center; and* [3]*Molecular and Integrative Physiological Sciences Program, Harvard School of Public Health, Boston, Massachusetts; and* [4]*Departments of Internal Medicine-Rheumatology and Neurology, University of Michigan Health System, Veterans Affairs Medical Center, Ann Arbor, Michigan*

Dyspnea (shortness of breath) and pain are well-evolved warnings of important physiological derangements that may require animals to alter their behavior to survive. Dyspnea and pain are also two of the most common symptoms that bring patients to medical care, another potentially adaptive behavior. Chronic dyspnea and pain, however, cause suffering and disability in many millions of patients; they often occur together in individuals. Although there has been great progress in recent decades in understanding the neurophysiology of pain, less is known about the neurophysiology of dyspnea, and even less is known about the interaction of these two symptoms. In the current issue of the *Journal of Neurophysiology* (p. 1396–1404), Morélot-Panzini and co-workers present a novel and interesting study showing that the presence of experimentally induced dyspnea inhibits a pain reflex. The results provoke us to think about both the commonality of pain and dyspnea pathways and about how they may interact.

For centuries people have applied noxious stimuli in one locale to inhibit the perception of pain in another location. There are several mechanisms through which endogenous analgesia can be elicited by competing noxious or stressful stimuli. Morélot-Panzini and co-workers present evidence showing that such analgesia can be induced using dyspnea (the perception of respiratory discomfort) as the analgesia-eliciting stimulus, rather than pain (Morélot-Panzini et al. 2006). They reason that dyspnea acts as a "counterirritant", and therefore it is a noxious sensation sharing some common neural pathways with pain. Dyspnea is a leading symptom of cardiopulmonary disease, and afflicts 50% of patients in tertiary care (equal to the symptom burden of pain).

Half a century ago a leading respiratory physiologist advised that "It might be profitable to compare the symptom dyspnea with the symptom pain" (Comroe 1956).Then, as now, the field of pain was further advanced than the field of dyspnea, due both to the number of researchers in the field, and to the added complexity of the physiological stimuli. A number of authors have echoed the pain-dyspnea analogy, but until this century the analogy was based only on the similarity of subjective characteristics. Recent brain imaging studies have shown that very similar cortical regions are activated by the perceptions of dyspnea and pain (Banzett et al. 2000; Evans et al. 2002; Peiffer et al. 2001), providing the first evidence that there is a neurophysiological link between these sensations. The study of Morélot-Panzini et al. takes an entirely different and novel approach to examine the neurophysiological connection between pain and dyspnea. We hope this will provoke other neurophysiologists to enter the fray.

Questions will arise in the reader's mind about some fundamental concepts and definitions. Pain is understood to be the perception of tissue damage, or impending tissue damage. Pain normally arises from stimulation of "nocioceptors" that signal "noxious" conditions, i.e., those that threaten harm. Dyspnea signals a threat to adequate pulmonary ventilation. Clearly, insufficient oxygen or excess carbon dioxide is a dramatic and immediate threat to tissues throughout the body, a noxious condition. The need for adequate oxygen and acid–base status is so great that the danger signal can be generated by a feed-forward mechanism that triggers the distress during conditions (airway obstruction, increased respiratory work) that predict an impending problem. It is reasonable to infer that survival under these conditions depends on immediate and focused attention to breathing; temporary inattention to most threats signaled by pain may be necessary. A burned hand is insignificant during suffocation.

In contrast to pain, which can be produced by stimulation of a single type of receptor in a single location, dyspnea most likely results from "imbalance" between levels of afferent signals that are normally present. For instance, if the cyclic inflation of the lungs (sensed by pulmonary stretch receptors) does not match the motor output of the brain stem respiratory centers (projected rostrally as "corollary discharge"), the unpleasant sensation of air hunger results (reviewed by Banzett and Lansing 1996). Excessive respiratory work or effort expended to cyclically inflate the lungs results in another unpleasant sensation – this latter phenomenon was employed by Morélot-Panzini and colleagues to evoke analgesia using external resistive loading of inspiration. Although most evidence suggests that the perception of dyspnea in this circumstance arises from muscle mechanoreceptors and perception of motor outflow (corollary discharge), the authors speculate that the observed analgesia arises from C-fibers in respiratory muscles or lungs via a subcortical mechanism of diffuse noxious inhibitory control (DNIC). While the effect demonstrated in this study is clear, this specific mechanism remains to be proven –

Address for reprint requests and other correspondence: R. B Banzett, Division of Pulmonary and Critical Care, Beth Israel Deaconess Medical Center, 330 Brookline Ave, Boston, MA 02215 (E-mail: dyspnea@hsph.harvard.edu).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

there are several alternative endogenous analgesic mechanisms that could be triggered by dyspnea. Pioneering efforts are seldom conclusive; we hope that future experiments from this group and others will define the mechanism, and by doing so advance our understanding of the neural mechanisms underlying dyspnea. One interesting experiment will be the comparison of strength of analgesia produced by an air hunger stimulus to that produced by a respiratory work stimulus. The sensation of air hunger appears to be more unpleasant than the sensation of excessive respiratory work (Lansing et al. 2000) but is not thought to involve C-fiber activation; thus if C fiber-driven DNIC is the analgesic mechanism, then air hunger should be a less potent analgesia-producing stimulus. Conversely, if the dyspnea-evoked analgesia depends on the noxiousness or unpleasantness of the stimulus, air hunger should be a more effective analgesia-producing stimulus. Morélot-Panzini et al. report preliminary observations in their discussion that an "air hunger" type stimulus did not appear to reduce the RIII response to a pain stimulus. These preliminary observations could be followed up with experiments in which the presence and degree of "air hunger" can be confirmed and its analgesic effects compared directly with "work and effort" of known magnitude.

Looking beyond the specifics of this particular phenomenon, the more general question of the nature of interaction between pain and dyspnea (mutual inhibition or facilitation) is important not only because of its physiological interest, but also because these two distressing symptoms frequently co-exist in patients. A published psychophysical study of the interaction of dyspnea and pain at the perceptual level showed that pain produced a small but consistent increase in perceived dyspnea, while dyspnea produced a larger but more variable decrease in pain (Nishino et al. 1999). The study of Morélot-Panzini and colleagues shows that this interaction may occur at the subcortical level. Both psychophysical and neurophysiological approaches will be needed to understand the similarities and interactions between these two troubling symptoms that frequently occur together in seriously ill patients.

REFERENCES

Banzett R, Lansing R. Respiratory sensations arising from chemoreceptors and pulmonary receptors: air hunger and lung volume. In: *Respiratory Sensation*, edited by Adams L and Guz A. New York: Marcel Dekker, 1996, p. 155–180.

Banzett RB, Mulnier HE, Murphy K, Rosen SD, Wise RJ, Adams L. Breathlessness in humans activates insular cortex. *Neuroreport* 11: 2117–2120, 2000.

Comroe JH. Dyspnea. *Mod Concepts Cardiovasc Dis* 25: 347–349, 1956.

Evans KC, Banzett RB, Adams L, McKay L, Frackowiak RS, Corfield DR. BOLD fMRI identifies limbic, paralimbic, and cerebellar activation during air hunger. *J Neurophysiol* 88: 1500–1511, 2002.

Lansing RW, Im BS, Thwing JI, Legedza AT, Banzett RB. The perception of respiratory work and effort can be independent of the perception of air hunger. *Am J Respir Crit Care Med* 162: 1690–1696, 2000.

Morélot-Panzini C, Demoule A, Straus C, Zelter M, Derenne J-P, Willer J-C, Similowski T. Dyspnea as a noxious sensation: inspiratory threshold loading may trigger diffuse noxious inhibitory controls in humans. *J Neurophysiol* 97: 1396–1404, 2006.

Nishino T, Shimoyama N, Ide T, Isono S. Experimental pain augments experimental dyspnea, but not vice versa in human volunteers. *Anesthesiology* 91: 1633–1638, 1999.

Peiffer C, Poline JB, Thivard L, Aubier M, Samson Y. Neural substrates for the perception of acutely induced dyspnea. *Am J Respir Crit Care Med* 163: 951–957, 2001.

INTERNATIONAL JOURNAL OF MEDICAL INFORMATICS 76 (2007) 407–411

journal homepage: www.intl.elsevierhealth.com/journals/ijmi

An 'Honest Broker' mechanism to maintain privacy for patient care and academic medical research

Andrew D. Boyd[a,b], *Charlie Hosner*[c], *Dale A. Hunscher*[c], *Brian D. Athey*[a,b], *Daniel J. Clauw*[c], *Lee A. Green*[d,*]

[a] *Department of Psychiatry, University of Michigan Medical Center, Ann Arbor, MI, USA*
[b] *Michigan Center for Biological Information, Office of Vice President of Research, University of Michigan, Ann Arbor, MI, USA*
[c] *Center for the Advancement of Clinical Research, University of Michigan Medical Center, Domino's Farms, Ann Arbor, MI, USA*
[d] *Department of Family Medicine, University of Michigan Medical Center, 1018 Fuller St., Ann Arbor, MI 48109-0708, USA*

ARTICLE INFO

Keywords:
Computer security
Computer communication networks
Medical records systems
Computerized
Honest Broker (non-mesh terminolgy)
Data integration (non-mesh terminolgy)

ABSTRACT

Purpose: From the Hippocratic Oath to the World Medical Association's Declaration of Geneva, physicians have sworn to protect patients' privacy. However, as systems move to more integrated architectures, protecting this medical data becomes more of a challenge. The increase in complexity of IT environments, the aggregation of data, and the desire of other entities to access this data, often 24 h/day × 7 day/week × 365 day/year, is putting serious strains on our ability to maintain its security. This problem cuts across all electronic record sources from patient care records to academic medical research records.

Approach: In order to address this issue, we are rethinking the way we store, transmit, process, access, and federate patient data from clinical and research applications. Our groups at the University of Michigan are developing a system called the "Honest Broker" to help manage this problem. The Honest Broker will offload the burden of housing identifiable data elements of protected health information (PHI) (e.g., name and address) as well as manage data transfer between clinical and research systems. Lab results and other non-identifiable data will be stored in separate systems with either a research study ID or clinical ID number. This two-component architecture increases the burden on attackers who now need to compromise two systems, one of which is seriously hardened, in order to match health data with a patient's actual identity.

Conclusions: While no security system is truly intrusion-proof, this architecture provides a high security choke point reducing the likelihood of a breach. By redesigning the method of integrating clinical care and research, we have enabled projects that would be cost prohibitive to conduct otherwise. The scalability of this mechanism is dependant on nature of the heterogenous nature of the clinical systems serving patients.

1. Introduction

Physicians have taken oaths to protect patients' privacy. Going back to Hippocrates, physicians have promised to keep the information gathered during the course of treatment private [1]. There are also a great many regulations that apply to protecting patients' information [2,3]. As medicine progressed, physicians began recording observations and treatment data

* *Corresponding author*. Fax: +1 734 998 7335.
E-mail address: greenla@umich.edu (L.A. Green).
1386-5056/$ – see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijmedinf.2006.09.004

on paper for future reference and review. From the first call to record results by Nightingale [4], recording the details of medical treatment has become the standard. Once that data was crystallized in physical form to protect the patient's privacy, it became subject to a variety of security problems, such as accidental loss, disclosure, theft, or destruction. Securing a paper record, while not a trivial task, does have some tried and true methods. Paper records' advantage is that the attacker needs to be physically present to access the data. However, paper records have their own risks [5].

With the introduction of computers into the health care environment, we have experienced a movement to store patient records electronically [6]. From the earliest days of computer storage, data protection has been addressed [7]. Securing the records on mainframe computers had documented risks; an unauthorized user who could gain access to a terminal had easy access to thousands of records. However, the world has become more complicated. Many of these non-networked mainframes have been replaced with networked client/server machines that provide theoretically ubiquitous access to the data stored therein. Now, we have expanded our attacker pool from proximate attackers to any attacker from a computer connected to the network. This introduces a new set of threats to electronic health records (EHRs). Many of the risks and benefits have been documented and discussed [8–10].

Historically, while medical data has been misused, medical databases specifically on the Internet have not been prime targets for illegal intrusions [11]. However, there have been numerous high profile releases of electronic medical records recently [12] as well as compiled in Anderson's book [13], and the trend and financial motive to target these types of data stores is increasing.

2. Background

The opportunity to provide enhanced patient care, or superior research, using aggregated data records and networking technology is very enticing. The most exciting potential of this data interchange is projects that are of direct benefit to patients while providing generalizable knowledge. There are several national and international initiatives to increase the connectivity of EHRs and to allow integration across departments, hospitals, and other care providers. An interesting demonstration of the many international efforts was Healthgrid 2005 [14], an international conference on health data integration. The US Department of Health and Human Services (DHHS) is funding technology prototypes of a National Health Information Network (NHIN) to share electronic health records between hospitals and clinics [15]. The United Kingdom is also investing billions of pounds in "Connecting for Health", which has the goal of creating a system of national electronic health records that can be seamlessly shared across the country [16]. The US National Institutes of Health (NIH) has also begun research into building a National Electronic Clinical Trials and Research (NECTAR) network allowing research subjects from different medical centers across the country to easily participate in large clinical trials [17]. The European Union (EU) is also promoting interoperability through their "e-Health" initiative, promoting the sharing of medical data across the EU [18]. The challenges of each of the above projects is different but all carry similar themes of increased complexity and network access to protected health information, which provides unique risks, some of which can be mitigated as outlined in SEISMED Consortium guidelines [19].

2.1. *Case study in health data integration*

As part of the NIH effort to "re-engineer the clinical research enterprise," we are linking together three clinical systems and one research system to support rigorous clinical research in the non-academically affiliated primary care practices of a regional practice-based research network (PBRN) [20]. The initial feasibility study will demonstrate the linked systems' ability to study depression and cardiovascular disease in non-academically affiliated primary care sites. Coronary heart disease patients will be identified either by events reported through the Cardiovascular Center's cooperative registry system or the PBRN practices' clinical problem list and reminder-generating system. Those who consent will be enrolled in the research study, and be tracked through the course of their participation in the study by the research support system and the Depression Center's monitoring system. They will complete psychometric instruments provided throughout their clinical courses. Outcomes will be collected from all three clinical systems and the results consolidated in the research system. Non-consenting patients will be offered clinical support through the Depression Center, and the problem list/reminder system will continue to manage their care, but their data will not be collected for the purpose of research.

In order to facilitate communication between the above systems, we are developing a method called the Clinical Research Information Fabric (CRIF), whose central component is called the Honest Broker (HB). Clinfotracker (the primary care system), M-STRIDES (the psychiatry system), M-CORRP (the cardiovascular system) and Velos (the research data collection system) will be able to use HB to share data securely and appropriately. The HB mediates between these systems and manages data transfer and electronic storage of personal health identifiers (ePHI) for them. Each patient is tracked in Honest Broker by an internally assigned unique ID that is mapped to corresponding patient identifiers in the participating systems. This matrix allows flow of de-identified patient data to the research system, but enables exchange of data between clinical systems without such systems needing to know any implementation details of the other system (see Fig. 1).

2.2. *Security mechanisms*

While each clinical system is responsible for its individual security profile, the methods of passing data between the systems is the focus of the security of the MCRC. Web Services are used to encode and send the messages between the clinical systems.

A specific example of this in our study is the depression monitoring program. Patients respond to an interactive voice recognition (IVR) questionnaire in M-STRIDES for depression severity symptoms; M-STRIDES then connects with the HB to pass the data to Clinfotracker and Velos. A successful attack

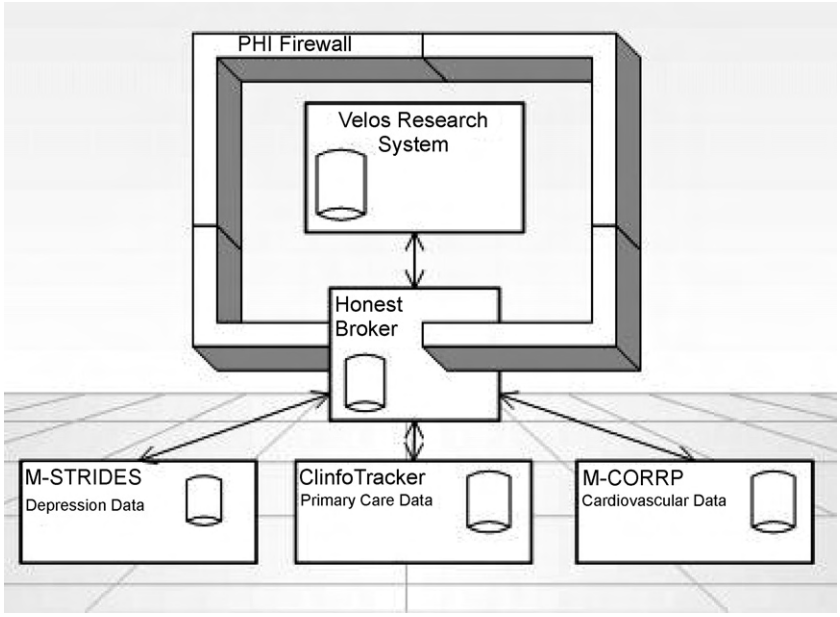


Fig. 1 – Michigan Clinical Research Collaboratory (MCRC).

on Velos will reveal all of the research medical data, but not expose any identification data. Additionally, successful attacks on the HB will reveal only names and arbitrary ID numbers, with no associated health data. Even if a system is compromised, the distributed nature of the data acts as an effective time-based security mechanism allowing administrators time to respond if the attack is detected. Due to the sensitive nature of the HB, severe limits on direct access to this system with hardening of the application, platform and procedures are necessary. Interactions between systems are automated and tightly restricted.

Each arrow in Fig. 1 represents a message between the computer systems. The data from the individual systems is transformed into XML messages, using HL7 standards when appropriate. The XML message is then wrapped into a Simple Object Access Protocol (SOAP) message and transmitted to the second system. After the second system received the message, the data is extracted in reverse order of the above encapsulation.

The security of data transmission is protected using a defense-in-depth strategy. First, the two communicating systems must authenticate each other, which is accomplished with the standard SSL handshake with dual authentication option. Authentication is done using X.509 certificates that are pre-installed on the communicating systems. Both the HB and the external system must identify, authenticate and authorize the other system before transmission will begin. The data transmission is protected using the battle-tested SSL protocol with a few changes to the default configuration. Instead of the typical server only authentication, both sides of the connection are authenticated. Weak algorithms (MD5) are disallowed in the configuration.

In addition to the above controls, traffic will be restricted to specific Internet Protocol (IP) addresses and data formats. No direct login to the Honest Broker system will occur during normal data transfer. All interaction is accomplished using the Web Services API that is hardened for exposure to the network.

Another concern is physical security. The servers are housed in a dedicated machine room with electronic locks, environmental controls, backup processes, and restricted personnel access. Off-site backups are stored in a physically secured, patrolled location.

3. Discussion

This project is small in scope compared to the larger initiatives at the national and international level, but has provided lessons-learned that can be useful in projects of larger scope. One key lesson is that matching records of individuals between hospitals and clinics with reliable certainty can be a challenge. Throughout our process we have a human confirm that the match is correct, that is, that the information from two or more systems actually belongs to the same patient, before making clinical decisions using that data. That human confirmation is possible because of the integration of the process into routine clinical care, allowing confirmation of identity to take place as a by-product of, for example, physician office visits. The match need be confirmed only once, and thereafter the Honest Broker's association of that patient's identifiers from the several systems will be reliable.

At the community scale, we can be confident that a majority of the patients will be easily covered by our identity match confirmation process. For example, in the medium-sized city where one of the test sites is developed, after hospital discharge almost all patients will be seen by physicians in the city or nearby towns. This however leaves out the patients who go to tertiary care facilities in the state or across the nation or world. Despite its challenges, scaling the Honest Broker to include other hospitals within the state is desirable, to allow

an increase in coverage of more information about potential patients or research subjects.

Where this model will deteriorate is trying to share clinical data across state or national boundaries. The challenge is the authority and authorization to practice medicine and report reliable data. Validating the credentials and authorization of remote users is a new level of complexity that will need to be added to the program to allow future expansion. This challenge can be solved by national credentialing services with appropriate legal agreements. Another challenge is there are no international patient identifiers. Biometric identifiers could help solve this problem, but would require a re-tooling of the healthcare establishment.

One facet of the project that is likely to scale across larger networks is that the Honest Broker holds only the necessary information to identify the individual across systems. There is no storage of actual health data, resolving some of the challenges of custodianship of medical data. Each network is still responsible for security and integrity of their health data.

A facet of the Honest Broker identity match confirmation model that is more difficult to scale to larger networks is determining who will be trusted to identify the individuals and record which clinics see which patients. Will one state or nation allow another to identify their patients? This is likely to lead to the creation of multiple Honest Brokers in countries or states, and to create the challenge of a new messaging and identification mechanisms between the Honest Brokers.

Also the policy issue of whether any clinician can pull up any record in any system are beyond the scope of this paper. Due to the realities of health care in the USA, a federated data model is necessary. Another scaling concern for countries that use a single aggregated database, is the interface to federated interface network. The largest issue is a paradigm change for the type of access to the data and whether current business processes support this type of data passing.

Another aspect of scaling the Honest Broker to larger networks is that using a trust hierarchy with local, regional, national, or international authentication will introduce a new security risk but will also decrease the need to maintain hundreds or thousands of keys for the Honest Broker. The risk model for the 'Honest Broker' will also need to be re-evaluated as the number of communicating institutions increases.

Finally, legal agreements to share data (e.g., HIPAA business agency agreements) are substantial hurdles to data sharing. Due to the limited number of institutions in our study, we have been able to solve the legal aspect of this project on a pairwise agreement basis. A challenge of exporting this model to a larger realm will be finding an efficient model for negotiating the legal agreements between the centers, either through a separate legal entity or standard language. A challenge on the international level is the differences in privacy laws between countries. For example EU Countries are unlikely to share medical data with the USA due to the lack to the same privacy protections [3].

3.1. *Recommendations for securing community wide health data*

From the experience above, the first recommendation about securing community wide health data is that security has to be incorporated in design efforts from the start. It must reside at the foundation of the analysis and design or it will not be effective; hence, our first security plan was finalized early in the development of our project. In building computer systems, many assumptions are made in early design stages that have profound effects on security down the road. If those assumptions and choices are not made with a security plan already in place, security will inevitably be compromised in later work.

The next recommendation is to use open standards and technologies, including open source software. Security by obscurity does not work. Any security system that relies on too many secrets is brittle and will crack. Use publicly tested architectures, technologies, and cryptography systems. Do not use a vendor if they refuse to disclose the inner workings of their security product.

The third recommendation is to create a comprehensive security system. Security is not a product or a point in space. It is best looked at as a chain or a fence. A chain is only as strong as its weakest link. Re-enforcing security components that are already strong and overlooking weak points is a common mistake. Take a global look at your system and identify threats and possible damages and the weakest parts, then spend resources to focus on those parts [19]. It is helpful to look to the security frameworks, such as the Health Insurance and Portability and Accountability Act (HIPAA) Security Rule [21], the SEISMED Consortium guidelines [19], and internationally the is ISO 17799 [22] for guidance.

The fourth recommendation is to hire dedicated security experts. Security requires special training and a special mindset. Security design, like other specialized fields, requires years of training and experience. The security field is complex and being relatively new, is changing at a rapid rate. Dedicated professionals have the tools and resources to design systems that stay ahead of attackers and provide adequate security combined with appropriate flexibility of function.

The fifth recommendation is to use either SHA-1, or SHA256 if possible, as the hash algorithm for any encryption needs. Avoid using MD5 which has been demonstrated to be insecure. While SHA-1 had a design level of protection of 2^{80}, recently discovered vulnerabilities have lowered the protection to 2^{63} [23]. Based on this news, new applications should only use SHA-1 if necessary and should implement SHA256 if possible.

The last recommendation is to realize that security is ever evolving. Static assets are at a severe disadvantage. Regularly reassessing threat vectors and updating security controls is needed to meet these new threats. We will review our security plan with every major release. Security is never done.

Acknowledgements

This project has been funded in whole or in part with Federal funds from the National Institutes of Health, under Contract No. HHSN268200425212C, "Re-Engineering the Clinical Research Enterprise"

REFERENCES

[1] Hippocrates, The Oath, 400 B.C.E. (http://classics.mit.edu/Hippocrates/hippooath.html, accessed September 15, 2005).

[2] Standards for Privacy of Individually Identifiable Health Information, U.S. DHHS. 67 Fed. Reg., vol. 157, Government Printing Office, Washington, DC, 2002, pp. 53181–53273.
[3] Council of Europe—Committee of Ministers Recommendation No. R(97)5 of The Committed of Ministers to Member States on the Protection Of Medical Data, Council of Europe Publishing, Strasbourg, February 1997.
[4] F. Nightingale, Notes on Hospitals: Being Two Papers Read Before the National Association for the Promotion of Social Science, at Liverpool in October 1858, with Evidence Given to the Royal Commissioners on the State of the Army in 1857, John W. Parker and Son, West Strand, London, 1859.
[5] A. Bakker, Security in perspective; luxury or must? Int. J. Med. Inform. 49 (1998) 31–37.
[6] R.S. Ledley, L. Lusted, Reasoning foundations of medical diagnosis, Science 130 (1959) 9–21.
[7] G.G. Griesser, et al., Data Protection in Health Information Systems, North-Holland Publishing Company, Amsterdam, 1980.
[8] Commission of the European Communities DGXIII/F AIM, Data Protection and Confidentiality in Health Informatics, IOS Press, Amsterdam, 1991.
[9] Council of Europe, Computerisation of Medical data in Hospital Services Including University Hospitals, Council of Europe Publications and Documents Divison, Strasbourg, 1988.
[10] B. Blobel, Analysis, Design and Implementation of Secure and Interoperable Distributed Health Information Systems, IOS Press, Amsterdam, 2002.
[11] CERT, Security of the Internet (http://www.cert.org/encyc_article/tocencyc.html#History, accessed September 20, 2005).
[12] J.H. Zamora, San Jose Arrest in theft of records South Bay patients' medical data stolen, San Francisco Chronicle (May) (2005) A-17.
[13] J.G. Anderson, K.W. Goodman, Ethics and Information Technology: A Case-Based Approach to a Health Care System in Transition, Springer-Verlag, New York, 2002.
[14] T. Solomonides, R. McClatchey, V. Breton, Y. Legre, S. Norager, From Grid to Healthgrid, IOS Press, Washington, DC, 2005.
[15] M. Leavitt, Developing a Prototype For A Nationwide Health Information Network Architecture, Department of Health and Human Services, Office of the National Coordinator for Health Information Technology (http://www.dhhs.gov/healthit/nhindemos.html, access September 16, 2005).
[16] Connecting for Health, National Programme for IT in the NHS (http://www.connectingforhealth.nhs.uk/, accessed September 20, 2005).
[17] E.A. Zerhouni, Re-engineering the Clinical Research Enterprise, National Institutes of Health (http://nihroadmap.nih.gov/clinicalresearch/overview-networks.asp, accessed September 16, 2005).
[18] Europe's Information Society, e-Health (http://europa.eu.int/information_society/eeurope/2005/all_about/ehealth/index_en.htm, accessed November 28, 2005).
[19] The SEISMED Consortium, Data Security for Health Care, User Guidelines, vol. III, IOS Press, Amsterdam, 1996, pp. 115–165.
[20] D. Lanier, Primary Care Practice-Based Research Comes of Age in the United States, Ann. Fam. Med. 3 (2005) S2–S4.
[21] Department of Health and Human Services, Health Insurance Reform: Security Standards, 45 CFR Parts 160, 162, and 164, February 20, 2003.
[22] International Organization for Standardization, ISO/IEC 17799 Information Technology Security Techniques (http://www.iso.org/iso/en/prods-services/popstds/informationsecurity.html, accessed November 28, 2005).
[23] X. Wang, Cryptanalysis of SHA-1 Hash Function, Cryptographic Hash Workshop National Institute of Standards and Technology, October 31, 2005 (http://www.csrc.nist.gov/pki/HashWorkshop/2005/Oct31_Presentations/Wang_SHA1-New-Result.pdf accessed November 30, 2005).

Arthritis Research & Therapy

Serum proteins and paraproteins in women with silicone implants and connective tissue disease: a case-control study

Arthritis Research & Therapy 2007, **9**:R95 doi:10.1186/ar2295

Gyorgy Csako (gcsako@nih.gov)
Rene Costello (RCostello@cc.nih.gov)
Ejaz A Shamim (shamime@ninds.nih.gov)
Terrance P O'Hanlon (ohanlont@mail.nih.gov)
Anthony Tran (anthony.tran@aphl.org)
Daniel J Clauw (dclauw@med.umich.edu)
H James Williams (James.Williams@hsc.utah.edu)
Frederick W Miller (millerf@mail.nih.gov)

ISSN 1478-6354

Article type Research article

Submission date 30 April 2007

Acceptance date 17 September 2007

Publication date 17 September 2007

Article URL http://arthritis-research.com/content/9/5/R95

Serum proteins and paraproteins in women with silicone implants and connective tissue disease: a case-control study

Gyorgy Csako[1], Rene Costello[1], Ejaz A Shamim[2], Terrance P O'Hanlon[2], Anthony Tran[1,3], Daniel J Clauw[4], H. James Williams[5] and Frederick W Miller[2]

[1]Department of Laboratory Medicine, Clinical Center, NIH, DHHS, 9000 Rockville Pike Bethesda, MD, 20892 USA

[2]Environmental Autoimmunity Group, National Institute of Environmental Health Sciences, NIH, DHHS, 9000 Rockville Pike, Bethesda, MD, 20892 USA

[3]Current address: Association of Public Health Laboratories, Silver Spring, MD, USA

[4]Division of Rheumatology, Department of Medicine, University of Michigan Medical School, 101 Simpson Dr, Ann Arbor, MI, 48109 USA

[5]Division of Rheumatology, Department of Internal Medicine, University of Utah Medical Center, 50 North Medical Dr., Salt Lake City, UT, 84132 USA

Corresponding author:

G. Csako, DLM, CC, NIH, Bldg. 10, Rm. 2C-407, 9000 Rockville Pike, Bethesda, MD 20892-1508, USA, gcsako@nih.gov

Abstract

Prior studies have suggested abnormalities of serum proteins, including paraproteins, in women with silicone implants but did not control for the presence of connective-tissue disease (CTD). This retrospective case-control study, performed in tertiary-care academic centers, assessed possible alterations of serum proteins, including paraproteins, in such a population. Seventy-four women with silicone implants who subsequently developed CTD and 74 age- and CTD-matched women without silicone implants were assessed in the primary study; other groups were used for additional comparisons. Routine serum protein determinations and high-sensitivity protein electrophoresis and immunofixation electrophoresis were performed for detection of paraproteins. Women with silicone implants, either with or without CTD, had significantly lower serum total protein and alpha-1, alpha-2, beta, and gamma globulins, and IgG levels compared to those without silicone implants. There was no significant difference, however, in the frequency of paraproteinemia between women with silicone implants and CTD (9.5%) and age- and CTD-matched women without silicone implants (5.4%) (OR 1.82 [95% CI 0.51 to 6.45]). Paraprotein isotypes were similar in the two groups and the clinical characteristics of the 13 women with paraproteinemia were comparable to an independent population of 10 women with silicone breast implants, CTD and previously diagnosed monoclonal gammopathies. In summary, this first comprehensive study of serum proteins in women with silicone implants and CTD found no substantially increased risk of monoclonal gammopathy. Women with silicone implants, however, had unexpectedly low serum globulin and immunoglobulin levels, with or without the subsequent development of CTD. The causes and clinical implications of these findings require further investigation.

Introduction

Local adverse effects from silicone implants, which include surgically placed devices as well as injections of liquid silicone, are well recognized [1-2], but systemic effects are not supported by current studies. Systematic reviews [3,4] and four meta-analyses including data from up to 20 retrospective cohort, case-control and cross-sectional studies [5-8] have failed to find significantly increased risks of any CTD after receiving silicone implants.

Few studies, however, have evaluated serum proteins and paraproteins in women with silicone implants. Plasmacytomas have been induced with silicone gel from breast implants in susceptible mouse strains [9] and several uncontrolled clinical reports suggested that silicone implants might be associated with multiple myeloma (MM) and its possible precursor, monoclonal gammopathy of undetermined significance (MGUS) [10-12]. One investigation evaluated the risk for MGUS in a retrospective case-control study of women with and without silicone implants and found a nonsignificant increase (odds ratio, OR 1.25 [95% CI 0.27-6.39]) [13]. Another case-control study found no increase in immunoglobulin levels or other immunologic parameters, with the exception of anti-ssDNA autoantibodies, in women with silicone implants [14]. None of these studies, however, assessed the role of concomitant CTD, which has been reported to be a risk factor for monoclonal immunoglobulins (paraproteins) and is associated with MGUS in 3-6% of cases [15].

The possible increased risk of paraproteins in women with silicone implants and CTD, as well as the limited information on other serum proteins in this population, prompted us to assess if silicone implants in women who subsequently developed CTD are associated with altered serum protein profiles and/or a higher prevalence of serum paraproteins.

Materials and methods

Patients and study design

All patients were enrolled prospectively in studies of the pathogenesis of the diseases described and extensive clinical information was collected at enrollment to assure subjects met diagnostic criteria. The current study was retrospective in that subjects enrolled in the prior studies were identified based on the presence of a stored serum sample.

The primary study population (Group 1) included 74 women who developed CTD after silicone implants and were enrolled in studies of the pathogenesis of CTD developing after silicone implants at the FDA and NIH from 1993-2000. These subjects were matched to 74 age- and CTD-matched women without silicone implants (Group 2) enrolled in other protocols at the FDA and NIH between 1993-2000 and subjects from a study of the underlying mechanisms of primary fibromyalgia (fibromyalgia syndrome, FMS) from 1986-89 and from the Early Undifferentiated Connective Tissue Disease study as part of the Cooperative Systematic Studies of the Rheumatic Diseases and enrolled between 1982 and 1987. We also matched 14 women with silicone implants but no CTD (Group 3) to 14 women without silicone implants or CTD (Group 4) for exploratory evaluations of the effects of silicone implants without CTD. In other exploratory analyses, cases from Group 2 that were found to have paraproteins were compared to those in independent groups of 28 women with CTD but without silicone implants (Group 5), and to 10 women with CTD and previously diagnosed gammopathies following silicone breast implants (Group 6). Apart from Group 6, none of the women had been diagnosed with paraproteinemia previously. All women gave informed consent to allow their clinical information and serum to be used for research purposes in clinical studies approved by institutional review boards at the U.S. FDA, NIH, Georgetown University, Washington, DC, and University of Utah, Salt Lake City, UT.

Disease classification criteria

Clinical diagnoses for CTD were determined following American College of Rheumatology (ACR) criteria or were based upon proposed criteria when ACR criteria were not available for a given condition. Patients with the following diseases were included in the analyses: definite or probable polymyositis (PM) or dermatomyositis (DM) [16], systemic sclerosis (SCL) [17], systemic lupus erythematosus (SLE) [18], FMS [19], and undifferentiated CTD (UCTD) and unexplained polyarthritis (UPA) [20]. Disease duration was defined as the time between onset of disease and specimen collection.

Selection of women with silicone implants for case-control study

As described above, 88 women (Groups 1 and 3), enrolled into FDA and NIH protocols investigating the pathogenesis of CTD following silicone implants, were chosen for study on the basis of the presence of documented silicone implants and an available serum sample collected for research purposes. Silicone implants consisted of surgically placed devices and liquid silicone injections. The most common types of silicone implants were breast implants (n=81); these included silicone gel filled devices (n = 68), saline implants (n = 6), both polyurethane and silicone gel implants (n = 3), and both polyurethane and saline implants (n = 4). Two women with breast implants also had additional silicone implants (one had liquid silicone injections and one had bilateral cheek implants). Five women received only silicone cheek implants. The time of silicone exposure was defined as the time from placement or injection of the first implant to specimen collection. Silicone implants duration was defined as the time from placement of the first implant to removal of the last implant.

Selection of women without silicone implants for the case-control study

Women without silicone implants consisted of subjects enrolled into investigations into the natural history of CTD diseases conducted at the FDA and NIH, the pathogenesis of FMS at Georgetown University and women enrolled in a multicenter inception cohort of early undifferentiated CTD (UCTD) who were followed to assess ultimate clinical outcomes [20]. The 88 women with silicone implants (Groups 1 and 3) were randomly matched for age and specific CTD (or, as appropriate, for lack of CTD) with women from these populations without silicone implants (Groups 2 and 4). Seventy-five patients (85%) were matched within 5 years of age; 12 patients (14%) were matched within 6 to 10 years, and 1 patient (1%) was matched within 15 years of age. The mean age was 50.2 $\pm$ 8.8 years (median 50, range 30-76) in the silicone implants group vs. 49.4 $\pm$ 8.4 years (median 50, range 32-71) in those without silicone implants ($p=0.06$). The women were also matched for diagnosis (64 with various inflammatory CTDs, 10 with non-inflammatory CTD [FMS]), and 14 without any CTD in both groups). Except for the single SLE subject with silicone implants, who was matched with a DM subject without silicone implants, all matched subjects shared the same clinical diagnoses. Diagnostic categories (and the total number of matched women) included UCTD (n=78), PM/DM (n=27), FMS (n=20), SCL (n=20), UPA (n=2), SLE (n=1), and no CTD (n=28). The frequencies of UCTD criteria in the silicone group were: unexplained polyarthritis 72%, myalgias 59%, isolated keratoconjunctivitis sicca 38%, Raynaud's 31%, rash 31%, central nervous system symptoms 13%, pulmonary symptoms 5%, elevated erythrocyte sedimentation rate 5%, false positive serologic test for syphilis 5% and peripheral neuropathy 3%. Although attempts were made to race-match whenever possible, there were more African-Americans and Hispanics in women without silicone implants (69 Whites/14 Blacks/3 Hispanics/1 Oriental/1 Unknown race) than in those with silicone implants (87 Whites/1 Hispanic).

Determination of serum total protein and immunoglobulins

Serum samples were stored at -80° C until analysis and laboratory personnel were blinded to the group identity of the samples. Total serum protein was measured by a biuret method on Hitachi 917 automated chemistry analyzers (Roche Diagnostics, Indianapolis, IN). Serum immunoglobulin G (IgG), IgA, and IgM levels were quantified by immunonephelometry on a Protein Array automated immunochemistry analyzer (Beckman-Coulter, Brea, CA).

Serum protein electrophoresis

For quantification of various protein fractions and paraprotein bands, all sera were first electrophoresed in agarose gel by a semi-automated electrophoretic system (SPIFE™ SPE Vis-60; Helena Labs., Beaumont, TX). After staining with amido black, gels were scanned with an EDC densitometer (Helena) at 545 nm. As part of the immunofixation electrophoretic screen for paraproteins (see below), all sera were also electrophoresed in agarose gel (Hydragel) by another semi-automated electrophoretic system (Hydrasys; Sebia, Norcross, GA). This screen involved the use of a more sensitive protein stain (acid violet) for improved detection of paraproteins.

Serum immunofixation electrophoresis (IFE)

After electrophoresing the sera in agarose gel (Hydrasys, Sebia), immunofixation was performed first with a mixture of antibodies (anti-α, γ, and μ heavy chain, and anti-κ and λ free light chain; Penta screen, Sebia). Patterns were visualized by staining with a highly sensitive protein stain (acid violet). All patterns considered positive or suggestive for the presence of paraproteins prompted full IFE work-up using the Hydrasys with acid violet staining. Two-thirds of the

specimens with positive findings for paraprotein(s) were also confirmed by a conventional manual IFE method involving the use of Paragon Blue stain (Paragon; Beckman-Coulter).

Statistical analyses

Data are shown as mean $\pm$ 1 standard deviation (SD). Statistically significant differences between groups were assessed with paired *t*-test, or McNemar test as deemed appropriate. OR and 95% CI were calculated by standard methods. All p values are 2-tailed and a p value of < 0.05 was considered significant.

Results

Characteristics of women in the case-control study with CTD

The time between placement of the first silicone implants and collection of the blood specimen for testing ("silicone exposure") was 15.4$\pm$7.3 (median 15.8) years for 86 assessable cases and the implant duration was 12.8$\pm$5.6 (median 12.9) years for 48 assessable cases. Of women with silicone implants who were available for assessment (n=63), 52% (33/63) likely had implant rupture based on magnetic resonance imaging (MRI, n=5) or signs and symptoms suggestive of rupture, such as the acute development of pain in the implant site or sudden changes in the size, shape or consistency of the implant (n=27), of which 17 ruptures were documented at surgery. Silicone breast implants were removed at least once in 67% of the 74 cases who were available for assessment: once in 55%, twice in 5%, and three-times in 7% of these cases. The mean$\pm$ SD duration of CTD was 6.8$\pm$6.6 (median 4.2) years for the 64 assessable cases in Group 1.

Serum protein profiles

Regardless of the presence or absence of CTD, there was a trend toward lower levels of total protein and various globulin fractions in women with silicone implants (Fig. 1). The total protein and all globulin fractions (alpha-1, alpha-2, beta, and gamma globulins) and IgG levels were significantly lower ($p<0.05$) in women with silicone implants compared to those without silicone implants in both the presence and absence of CTD (Fig. 1). IgA and IgM levels were also significantly lower ($p<0.05$) in women with silicone implants who developed CTD (Group 1) compared to matched women without silicone implants who developed CTD (Group 2). These differences were less often significant in women without CTD (Group 3 vs. Group 4) although these samples sizes were smaller. Only albumin failed to show significantly lower levels with silicone implants exposure either in the presence or absence of CTD. Apart from fewer significant differences between groups of women with FMS, the results were also similar when women with/without silicone implants were compared in subsets of inflammatory CTDs (64 pairs) and FMS (10 pairs) from Groups 1 and 2 (data not shown).

Serum paraproteins

No paraproteins were found in women without CTD either in the presence (Group 3) or absence of silicone implants (Group 4). Paraproteins were also relatively uncommon in the sera of women with CTD, either with silicone implants (Group 1) or without silicone implants (Group 2) (Table 1). Full immunofixation electrophoresis workups revealed no significant difference in paraproteinemia rates between women with silicone implants (7/74 or 9.5%) (Table 2) and without silicone implants (4/74 or 5.4%) (Table 3) (OR 1.82 [95% CI 0.51-6.45]). Five of the 7 women with CTD, silicone implants and paraproteinemia had UCTD but there were no significant differences ($p=0.55$) in the CTD diagnostic distribution patterns between those with

and without silicone implants (Table 1). There was only a single case of paraproteinemia in women with FMS and this case occurred in a subject with silicone implant (Table 1). Because of the concern that only inflammatory CTDs might be associated with paraproteins, we also compared only the non-FMS cases. After omitting the 10 pairs of cases of FMS from the analysis, there was no significant difference in the frequency of paraproteins between the remaining 64 women with inflammatory CTDs and silicone implants (6 cases) and the matched 64 women with inflammatory CTDs without implants (4 cases). Of interest, many women with silicone implants and paraproteinemia likely had implant rupture (Table 2). While the women with silicone implants and paraproteinemia (Table 2) were older than those without silicone implants (Table 3), the difference did not reach statistical significance ($p = 0.26$) and the age difference completely disappeared when only women from Groups 1 and 2 were compared. Within the group of women with silicone implants and CTD (Group 1), there were only borderline significant or no significant differences (Mann-Whitney U-test) in age (55.6 vs. 49.3 years, $p = 0.041$), duration of CTD (10.4 vs. 6.4 years, $p = 0.051$), implant duration (10.2 *vs*. 12.5 years, $p = 0.267$), and duration of silicone exposure (16.1 *vs*. 15.4 years, $p = 0.783$), between those with and those without paraproteins. After omitting the 10 cases of FMS, the remaining 64 pairs of women with inflammatory CTDs exhibited similar patterns (data not shown). Further, irrespective of including or excluding cases of FMS, there were no significant differences in age between those with and those without paraproteins within the group of women with CTD but no silicone implant (Groups 2 and 5) (data not shown).

The paraprotein isotypes were similar in women with and without silicone implants and included IgG(κ), IgG(λ) and IgM(λ) (Table 1). However, while every subject with paraproteinemia in the silicone implant group had only a single band, this was not true in the comparison group without

silicone implants. In this latter group, one woman with DM had two IgG(κ) bands and one IgG(λ) band and a woman with PM had both IgG(κ) and IgM(λ) bands. Consequently, the total number of paraprotein bands was the same in the two study groups (Table 1). All paraproteins occurred in low concentrations. Only an IgG(κ) band was quantifiable (estimated serum concentration from the protein electrophoretic pattern: $\underline{\sim}$ 1 g/L), all others had trace quantities (< 1 g/L estimated concentration from protein electrophoresis) (Table 2). No subject with paraprotein(s) developed multiple myeloma or other malignancy during the 2-year follow-up period after enrollment in the study.

Comparison of women with paraproteinemia in other study groups

To assess if the paraproteinemia cases identified in the case-control studies were different from those in independent populations, women with paraproteins in the case-control studies were compared to those from another group of 28 women with CTD without silicone implants (Group 5), and to 10 women with silicone implants and previously diagnosed paraproteins (Group 6) (Table 4). Since the two cases of paraproteinemia identified from Group 5 were comparable in age, paraprotein type and frequency (2/28 or 7.1%) to those identified from the CTD patients with no silicone implants in the case-control study (Group 2), they were combined for further analysis (Table 3). This group of six women with CTD and paraproteinemia but no silicone implants was similar in age (mean 49.7 years) to the 10 women with CTD, silicone implant exposure and previously diagnosed paraproteinemia (MGUS or MM) (Group 6, mean age 50.8 yrs) (Table 4). However, the seven women with CTD, silicone implant exposure and paraproteinemia were older (mean 55.6 yrs) than either of the previous groups (Table 2). The paraprotein types identified in these women (Table 2) were similar to the other two groups of

women with paraproteinemia (Tables 3 and 4), and UCTD was the most common clinical diagnosis associated with paraproteinemia in all 3 groups. Serum protein profiles for women with paraproteinemia revealed similar albumin levels in all three groups. Except for IgG and gamma globulin levels in the previously diagnosed MGUS/MM group with CTD and silicone breast implants (Group 6), various protein fractions tended to be lower in those with silicone implants than without silicone implants (Fig. 2).

Discussion

The limited number of studies of serum proteins and paraproteins in women with silicone implants, and the lack of a controlled study taking into account CTD as an additional possible risk factor for serum protein abnormalities, prompted this case controlled investigation. Paraproteinemia is most often associated with MGUS that in turn may be a precursor of multiple myeloma, macroglobulinemia, amyloidosis or related diseases [21]. Subjects with MGUS often have autoantibodies [22] or autoimmune manifestations [23] and subjects with rheumatic diseases are reported to have higher rates of MGUS [15]. Therefore, a critical aspect of our case-control study design was to match subjects not only by age, but also by CTD diagnosis to minimize possible confounding. We also used highly sensitive agarose gel electrophoretic and immunofixation electrophoresis methods to maximize detection of serum paraproteins. Because it is possible that FMS patients may differ from inflammatory CTDs in the risk of paraproteinemia, we analyzed the women in each group without FMS and found that excluding them does not alter the primary findings of the study.

Although serum paraproteins occurred somewhat more frequently in our study of 88 women (74 with CTD) and silicone implants compared to those without silicone implants (8.0% *vs*. 4.5%), the difference was not statistically significant. Further, since all paraproteins occurred at very low serum concentrations ($\leq$1 g/L), our cases likely represent MGUS [24]. Without additional testing (including bone marrow biopsy, urinary free light chain assessment, chromosomal studies and bone surveys) and without follow-up regarding the persistence of paraprotein bands [21,23-28], we could not completely rule out an ongoing malignant process. Nevertheless, none of the subjects reported progression to multiple myeloma or other hematologic malignancies for up to 2 years after study enrollment. Overall, our findings do not support a major role for silicone implants in inducing monoclonal gammopathies in humans and are consistent with conclusions of prior investigations of silicone implants and MGUS [13,14] or MM [9-31].

We observed higher prevalences of paraproteinemia in women with CTD both with and without silicone implants (8.0% and 4.5%, respectively) than those reported for similarly aged women with any type of breast implants (1.4% to 1.7%) in one study [14]. Our prevalence rates of paraproteinemia, however, were lower than reported by the same authors for similarly aged women with breast implants (10.4% to 15.8%) in another study (16). MGUS is known to increase in prevalence with age, but our observed prevalence rates are higher than those reported in the literature for "healthy" adult subjects/populations of up to >70 years of age (0.5-3.0%) [32-34]. Our finding of 3 to 5-times higher prevalence of serum paraproteins over those expected for our age group in the case-control study is, in part, likely related to the combined use of both a highly sensitive protein stain and highly sensitive IFE. Using similar analytical methods (Helena agarose electrophoresis and Sebia IFE), Kyle *et al.* [35] recently reported a relatively high (3.2%) prevalence of MGUS in a population-based study of 21,463 subjects $\geq$50 years of age. The age-

adjusted rates of MGUS were significantly higher in men than women (4.0 vs. 2.7%) and the prevalence of MGUS increased with age to 5.3% in subjects $\geq$ 70 years. Since these rates are approximately twice that observed earlier, they suggest that the screening methods used in many previous studies were less sensitive than current techniques [35]. In addition to using highly sensitive detection techniques, the high prevalence of paraproteinemia in our study may also be related to the reportedly high prevalence (~3-6%) of paraproteins in subjects with CTD [15] and the relatively high prevalence of CTD (6%) in subjects with MGUS [22]. Regardless of silicone implant exposure, all of our newly identified paraproteinemia cases occurred in women with CTD, resulting in an overall 7.4% prevalence in this group (13/176).

While the total number of cases with paraproteinemia was small in our study, we also observed biclonal cases more often (15% or 2 out of 13 paraproteinemia cases) than expected from previous investigations in the general population (~2% of MGUS cases) [31,36,37]. Interestingly, both of our biclonal cases occurred in myositis subjects with no silicone implants. The distribution of heavy chain types of the serum paraproteins identified in our study for women with silicone implants and CTD in all 13 cases combined was similar to that we found in women with silicone implants, CTD and previously diagnosed paraproteins, and in those described in earlier MGUS case series (71-73% *vs.* 83% for IgG, and 11-14% *vs.* 17% IgM in our population) [13,14,31,36]. We found no IgA paraprotein (0% vs. 11-14% in earlier reports for MGUS [31,36] but this may be due to our comparatively small sample size.

The etiology of MGUS and MM is poorly understood, but case reports and epidemiological studies have shown an increased association with chronic inflammatory conditions [12,38]. Autonomous growth with clonal B-cell expansion and selection mediated by chronic antigen

stimulation have been hypothesized to contribute to the development of MM. Silicone has been reported to trigger a variety of inflammatory and immunological (both humoral and cellular) responses in humans 3[9-42] and experimental animals [[43]. Experimentally, plasma cell tumors (peritoneal plasmacytomas) could be induced in up to 80% of genetically susceptible mice with intraperitoneal injection of silicone gels and oils [9,44]. It is unlikely that our inability to detect significantly increased numbers of paraproteinemia cases in conjunction with prior silicone implants in women with CTD was related to inadequate exposure to silicone. The 15.4-year mean duration of silicone implant exposure (median 15.8, range 0.9-31.3) in our case-control study approached the exposure time of women with previously diagnosed CTD and MGUS/MM (mean 17.4 yrs, median 16.8, range 10.2-29.0), and both groups had a high rate of implant rupture or leak ($\geq$52% and $\geq$71%, respectively).

Unexpected findings were the significantly lower serum total protein and alpha-1, alpha-2, beta, and gamma globulins, and IgG levels in those with silicone implants compared to those without silicone implants, in both the presence and absence of CTD. We have found no comprehensive study of the serum protein profile in silicone implants subjects in the literature and the results reported for selected serum proteins and/or protein fractions are conflicting. Hypergammaglobulinemia has been reported in both women with silicone implants [11,45] and in mouse models of silicone exposure [9,46]. In contrast, the total gammaglobulin levels in 2,721 consecutive women with silicone implants (47), and the IgG, IgA and IgM levels in 156 women with silicone implants and rheumatic disease complaints [48] were found to be normal. Furthermore, the proportions of increased or decreased IgG, IgA, and IgM levels between well-matched groups of 298 “healthy” women with and without breast implants were similar in the Women’s Health Study [14]. Our findings of lower gamma globulin and immunoglobulin levels

in women with silicone implants compared to women without implants are thus at variance with these earlier observations. Since all serum globulin fractions tended to be lower with silicone implant exposure in both healthy subjects and those with various CTD, CTD is an unlikely contributor and the etiology of this possible effect of silicone implants remains unclear and requires further study.

Limitations of our study include comparatively small sample sizes; heterogeneity of women regarding type and length of their silicone implant exposure and CTD diagnoses; lack of quantitative information regarding markers of autoimmune diseases; incomplete information regarding possible treatment effects (type and dose of medications); lack of data for the possible presence of abnormal urinary free light chains; unavailability of bone marrow studies; and lack of extended follow-up regarding the possible development of additional paraproteins and/or possible conversion into MM.

Conclusions

We found unexpected significant differences in the serum protein profiles of women with silicone implants compared to those without silicone implants, but no evidence for a substantially increased risk of paraproteinemia. From a public health point of view, silicone implants appear to have a minimal, if any, effect on the number of women in whom paraproteins may occur, even in the context of coexisting connective tissue disease.

Abbreviations

ACR, American College of Rheumatology; CTD, connective tissue disease; DM, dermatomyositis; FDA, (U.S.) Food and Drug Administration; FMS, fibromyalgia; IFE, immunofixation electrophoresis; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; OR, odds ratio; PM, polymyositis, SCL, systemic sclerosis (scleroderma), SLE, systemic lupus erythematosus; UCTD, undifferentiated CTD; UPA, unexplained polyarthritis.

Competing interests

The authors declare that they have no competing interests.

Author contributions

FWM, GC, DJC, HJW, TPO, and EAS designed the study; GC, FWM, RC, EAS, AT, TPO, DJC, and HJW acquired the data; GC, FWM, RC, and AT analyzed and interpreted the data; GC and FWM prepared the manuscript; and GC, FWM, and RC performed the statistical analysis.

Acknowledgments

Supported in part by the FDA Office of Women's Health and the intramural programs of the National Institutes of Health (Clinical Center and National Institute of Environmental Health Sciences). We wish to acknowledge the clinical assistance of Drs. Elham Bayat and Venkata Erella and the statistical assistance of Drs. James Malley, Karen Malley, and Robert Wesley. We thank Drs. Sahar Dawisha, Gregory Dennis, and Nadja N. Rehak for useful comments after reviewing the manuscript.

References

1. Gabriel SE, Woods JE, O'Fallon WM, Beard CM, Kurland LT, Melton LJ III: **Complications leading to surgery after breast implantation**. *New Engl J Med* 1997, **336**:677-682.
2. Kulmala I, McLaughlin JK, Pakkanen M, Lassila K, Holmich LR, Lipworth L, Boice JD Jr, Raitanen J, Luoto R: **Local complications after cosmetic breast implant surgery in Finland**. Ann Plast Surg 2004, **53**:413-419.
3. Park AJ, Black RJ, Watson AC: **Silicone gel breast implants, breast cancer and connective tissue disorders**. *Br J Surg* 1993, **80**:1097-1100.
4. Gerszten PC: **A formal risk assessment of silicone breast implants**. *Biomaterials* 1999, **20**:1063-1069.
5. Perkins LL, Clark BD, Klein PJ, Cook RR: **A meta-analysis of breast implants and connective tissue disease.** *Ann Plast Surg* 1995, **35**:561-570.
6. Wong O: **A critical assessment of the relationship between silicone breast implants and connective tissue diseases.** *Regul Toxicol Pharmacol* 1996, **23**:74-85.
7. Hochberg MC, Perlmutter DL: **The association of augmentation mammoplasty with connective tissue disease, including systematic sclerosis (scleroderma): a meta-analysis**. *Curr Top Microbiol Immunol* 1996, **210**:411-417.
8. Janowsky EC, Kupper LL, Hulka BS: **Meta-analyses of the relation between silicone breast implants and the risk of connective-tissue diseases**. *N Engl J Med* 2000, **342**:781-790.

9. Potter M, Morrison S, Wiener F, Zhang XK, Miller FW: **Induction of plasmacytomas with silicone gel in genetically susceptible strains of mice.** *J Natl Cancer Inst* 1994, **86**:1058-1065.

10. Tricot GJ, Naucke S, Vaught L, Vesole D, Jagannath S, Barlogie B: **Is the risk of multiple myeloma increased in patients with silicone implants?** *Curr Top Microbiol Immunol* 1996, **210**:357-359.

11. Garland LL, Ballester OF, Vasey FB, Benson K, Moscinski LC, Farmelo MJ, Rodriguez MJ, Rapaport DP: **Multiple myeloma in women with silicone breast implants. Serum immunoglobulin and interleukin-6 studies in women at risk**. *Curr Top Microbiol Immunol* 1996, **210**:361-366.

12. Silverman S, Vescio R, Silver D, Renner S, Weiner S, Berenson J: **Silicone gel implants and monoclonal gammopathies: three cases of multiple myeloma and the prevalence of multiple myeloma and monoclonal gammopathy of undetermined significance**. *Curr Top Microbiol Immunol* 1996, **210**:367-734.

13. Karlson EW, Tanasijevic M, Hankinson SE, Liang MH, Colditz GA, Speizer FE, Schur PH: **Monoclonal gammopathy of undetermined significance and exposure to breast implants**. *Arch Intern Med* 2001, **161**:864-867.

14. Karlson EW, Hankinson SE, Liang MH, Sanchez-Guerrero J, Colditz GA, Rosenau BJ, Speizer FE, Schur PH: **Association of silicone breast implants with immunologic abnormalities: a prospective study.** *Am J Med* 1999, **106**:11-19.

15. Broggini M, Cavallo A, Baratelli E, Volonte S, Crespi E, Cappelli A, Chelazzi G: [**Monoclonal gammopathy of uncertain significance in rheumatic disease**] *Recenti Prog Med* 1990, **81**:306-309. Italian.

16. Bohan A, Peter JB, Bowman RL, Pearson CM: **Computer-assisted analysis of 153 patients with polymyositis and dermatomyositis.** *Medicine (Baltimore)* 1977, **56**:255-286.

17. Masi A: **Classification of systemic sclerosis (scleroderma): relationship of cutaneous subgroups in early disease to outcome and serologic reactivity**. *J Rheumatol* 1988, **15**:894-898.

18. Hochberg MC: **Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus**. *Arthritis Rheum* 1997, **40**:1725.

19. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, *et al.*: **The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee**. *Arthritis Rheum* 1990, **33**:160-172.

20. Williams HJ, Alarcon GS, Joks R, Steen VD, Bulpitt K, Clegg DO, Ziminski CM, Luggen ME, St Clair EW, Willkens RF, *et al.*: **Early undifferentiated connective tissue disease (CTD). VI. An inception cohort after 10 years: Disease remissions and changes in diagnoses in well established and undifferentiated CTD**. *J Rheumatol* 1999, **26**: 816-825.

21. Kyle RA, Rajkumar SV: **Monoclonal gammopathy of undetermined significance**. *Clin Lymphoma Myeloma* 2005, **6**:102-114.

22. MacGregor AJ, Kalsi J, Ravirajan CT, Leaker B, Watts R, Winska-Wiloch H, Knight B, Norden A, Isenberg DA, Cambridge G: **Analysis of antibody reactivity in the sera of 42 patients with paraproteinemia.** *Autoimmunity* 1992, **13**:101-105.

23. Jonsson V, Svendsen B, Vorstrup S, Krarup C, Schmalbruch H, Thomsen K, Heegaard NH, Wiik A, Hansen MM: **Multiple autoimmune manifestations in monoclonal**

gammopathy of undetermined significance and chronic lymphocytic leukemia. *Leukemia* 1996, **10**:327-332.

24. Brigden ML: **The search for meaning in monoclonal protein. Is it multiple myeloma or monoclonal gammopathy of undetermined significance?** *Postgrad Med* 1999, **106**:135-142.

25. Bataille R, Chappard D, Basle MF: **Quantifiable excess of bone resorption in monoclonal gammopathy is an early symptom of malignancy: a prospective study of 87 bone biopsies**. *Blood* 1996, **87**:4762-4769.

26. Zandecki M, Lai JL, Genevieve F, Bernardi F, Volle-Remy H, Blanchet O, Francois M, Cosson A, Bauters F, Facon T: **Several cytogenetic subclones may be identified within plasma cells from patients with monoclonal gammopathy of undetermined significance, both at diagnosis and during the indolent course of this condition**. *Blood* 1997, **90**:3682-3690.

27. Konigsberg R, Ackermann J, Kaufmann H, Zojer N, Urbauer E, Kromer E, Jager U, Gisslinger H, Schreiber S, Heinz R, *et al.*: **Deletions of chromosome 13q in monoclonal gammopathy of undetermined significance.** *Leukemia* 2000, **14**:1975-1979.

28. Almeida J, Orfao A, Mateo G, Ocqueteau M, Garcia-Sanz R, Moro MJ, Hernandez J, Ortega F, Borrego D, Barez A, *et al.*: **Immunophenotypic and DNA content characteristics of plasma cells in multiple myeloma and monoclonal gammopathy of undetermined significance**. *Pathol Biol (Paris)* 1999, **47**:119-127.

29. McLaughlin JK, Fraumeni JF Jr, Olsen J, Mellemkjaer L: *Re: Breast implants, cancer, and systemic sclerosis.* [Letter] *J Natl Cancer Inst* 1994, **86**:1424.

30. McLaughlin JK, Fraumeni JF Jr, Nyren O, Adami HO: **Silicone breast implants and risk of cancer?** *JAMA* 1995, **273**:116.

31. Kyle RA: **Monoclonal gammopathy of undetermined significance**. *Curr Top Microbiol Immunol* 1996, **210**:375-383.

32. Colls BM: **Monoclonal gammopathy of undetermined significance (MGUS)-31 year follow up of a community study**. *Aust N Z J Med* 1999, **29**:500-504.

33. Axelsson U, Bachman R, Hallen J: **Frequency of pathological proteins (M-components) in 6,995 sera from an adult population**. *Acta Med Scand* 1966, **179**:235-247.

34. Saleun JP, Vicariot M, Deroff P: **Monoclonal gammopathies in the adult population of Finistere, France**. *J Clin Pathol* 1982, **35**:63-68.

35. Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF, Offord JR, Dispenzieri A, Katzmann JA, Melton LJ 3rd: **Prevalence of monoclonal gammopathy of undetermined significance.** *N Engl J Med* 2006; **354**:1362-1369.

36. Giraldo MP, Rubio-Felix D, Perella M, Gracia JA, Bergua JM, Giralt M: [**Monoclonal gammopathies of undetermined significance. Clinical course and biological aspects of 397 cases**] [Spanish] *Sangre (Barc)* 1991; **36**:377-382.

37. Nilsson T, Norberg B, Rudolphi O, Jacobsson L: **Double gammopathies: incidence and clinical course of 20 patients**. *Scand J Haematol* 1986; **36**:103-106.

38. Isobe T, Osserman EF: **Pathologic conditions associated with plasma cell dyscrasias: a study of 806 cases.** *Ann N Y Acad Sci* 1971; **190**:507-518.

39. Wolf LE, Lappe M, Peterson RD, Ezrailson EG: **Human immune response to polydimethylsiloxane (silicone): screening studies in a breast implant population.** *FASEB J* 1993; **7**:1265-1268.

40. Smalley DL, Shanklin DR, Hall MF: **Monocyte-dependent stimulation of human T cells by silicon dioxide**. *Pathobiology* 1998; **66**:302-305.

41. Zandman-Goddard G, Blank M, Ehrenfeld M, Gilburd B, Peter J, Shoenfeld Y: **A comparison of autoantibody production in asymptomatic and symptomatic women with silicone breast implants.** *J Rheumatol* 1999; **26**:73-77.

42. O'Hanlon T, Koneru B, Bayat E, Love L, Targoff I, Malley J, Malley K, Miller F; Environmental Myositis Study Group: **Environmental Myositis Study Group. Immunogenetic differences between Caucasian women with and those without silicone implants in whom myositis develops.** *Arthritis Rheum* 2004; **50**:3646-3650.

43. McDermott MR, Brook MA, Bartzoka V: Adjuvancy effect of different types of silicone gel. *J Biomed Mater Res* 1999; **46**:132-134.

44. Potter M, Morrison S: **Plasmacytoma development in mice injected with silicone gels.** *Curr Top Microbiol Immunol* 1996; **210**:397-407.

45. Schoaib BO, Patten BM, Calkins DS: **Adjuvant breast disease. An evaluation of 100 symptomatic women with breast implants or silicone fluid injections.** *Keio J Med* 1994; **43**:79-87.

46. Naim JO, Satoh M, Buehner NA, Ippolito KM, Yoshida H, Nusz D, Kurtelawicz L, Cramer SF, Reeves WH: **Induction of hypergammaglobulinemia and macrophage activation by silicone gels and oils in female A.SW mice**. *Clin Diagn Lab Immunol* 2000; **7**:366-370.

47. Lewy RI, Ezrailson E: **Laboratory studies in breast implant patients: ANA positivity, gammaglobulin levels, and other autoantibodies.** *Curr Top Microbiol Immunol* 1996; **210**:337-3353.

48. Bridges AJ, Conley C, Wang G, Burns DE, Vasey FB: **A clinical and immunologic evaluation of women with silicone breast implants and symptoms of rheumatic disease**. *Ann Intern Med* 1993; **118**:929-936.

FIGURE LEGENDS

Figure 1. Serum proteins and immunoglobulins in women with/without connective tissue disease (CTD) and with/without silicone implants. Box-plots: vertical lines identify 10^{th} and 90^{th} percentiles, horizontal lines in boxes identify 25^{th}, 50^{th} (median), and 75^{th} percentiles, while "outliers" are shown with open symbols. Abbreviations: Ref. (filled columns), reference intervals; CTD+ and S-, Group 2 (74 women with CTD but no silicone implants); CTD+ and S+, Group 1 (74 women with CTD and silicone implants); CTD- and S-, Group 3 (14 women with no disease and no silicone implants); CTD- and S+, Group 4 (14 women with no disease but silicone implants). NS, not significant; *p<0.05, **p<0.01, ***p<0.001, and ****p<0.0001 using paired *t*-test.

Figure 2. Serum proteins and immunoglobulin levels in women with CTD and paraproteinemia with/without silicone implants. Abbreviations: Ref. (filled columns), reference intervals; S- (open circles), six women from Groups 2 and 5 with CTD but no silicone implants (see Table 3); S+ (open triangles), seven women from Group 1 with CTD and silicone implants (see Table 2); and S+M, (open rectangles), ten women (Group 6) with CTD, silicone breast implants and previously identified paraproteinemia (see Table 4).

Table 1. Serum paraproteins in the case-control study of 74 age- and connective tissue disease diagnosis-matched women with and without silicone implants.

	Silicone implant	
	Yes (Group 1)	No (Group 2)
Age*	49.9 ± 8.7 years	49.8 ± 8.4 years
Number of women with paraprotein band(s)/total**	7/74 (9.5%)	4/74 (5.4%)
Number of women with paraprotein band(s) according to primary CTD diagnosis		
UPA	0/1 (0%)	0/1 (0%)
SCL	1/10 (10%)	0/10 (0%)
SLE	0/1 (0%)	0/0 (0%)
PM/DM	1/13 (4%)	2/14 (4%)
UCTD	4/39 (13%)	2/39 (5%)
FMS	1/10 (0%)	0/10 (10%)
Type of paraprotein band(s)***		
IgG(κ)	4	5
IgG(λ)	1	1
IgM(κ)	0	0
IgM(λ)	2	1

Abbreviations: unexplained polyarthritis, UPA; fibromyalgia syndrome, FMS; systemic sclerosis, SCL; systemic lupus erythematosus, SLE; polymyositis/dermatomyositis, PM/DM; and undifferentiated connective tissue disease, UCTD

*Age mean ± SD, no significant difference by paired *t*-test (p=0.82).

**No significant differences between Groups 1 and 2 using McNemar test (p=0.55).

***One woman with dermatomyositis had two IgG(κ) and one IgG(λ) bands, whereas a patient with polymyositis had both IgG(κ) and IgM(λ) bands.

Table 2. Characteristics of women with connective tissue disease and silicone implants in whom paraproteinemia was identified from Group 1. Subjects are listed in increasing order of age *

Age (yrs)	Connective tissue disease		Silicone implant				Serum paraprotein** (Isotype)
	Type	Duration (yrs)	Type	Duration (yrs)	Exposure (yrs)	Rupture***	
48	UCTD	15.4	silicone gel, saline	17.7	18.0	yes	IgM(λ)
49	FMS/UCTD	15.2	silicone gel (chin)	6.0	17.7	yes	IgG(κ)
53	UCTD	6.2	saline	3.5	3.5	yes	IgG(λ)
55	SCL	12.1	polyurethane	4.3	16.1	n/a	IgG(κ)
60	UCTD/FMS	3.9	silicone gel	20.1	24.2	yes	IgG(κ)
61	DM	4.2	silicone gel	10.0	10.2	yes	IgG(κ)
63	UCTD	16.1	silicone gel	n/a	23.3	yes	IgM(λ)
All:	55.6 ± 5.9	10.4 + 5.5		10.3 ± 7.1	16.1 ± 7.3		

Abbreviations per Table 1; n/a, not available

* All subjects were White.

**Based on protein electrophoresis, all paraprotein bands were considered weak (defined as <1 g/L).

*** Implant rupture was suspected by signs and symptoms in six cases and documented at surgery in four cases.

Table 3. Characteristics of women with connective tissue disease but without silicone implants in whom paraproteinemia was identified from Group 2 and Group 5 (Italicized cases). Subjects are listed in increasing order of age.

Age (yrs)	Ethnicity	Connective tissue disease	Serum paraprotein (Isotype)*
32	Hispanic	UCTD	IgG(κ)
43	White	PM	IgG(κ)
47	Hispanic	UCTD	IgG(κ)
55	White	DM	IgG(κ) x2, IgG(λ)
56	Black	PM	IgG(κ), IgM(λ)
65	White	UCTD	IgG(κ)

All: 49.7 ± 11.6 (Group 2 patients only [n=4]: 55.8 ± 7.4)

Abbreviations per Table 1

*Based on protein electrophoresis, all paraprotein bands were considered weak (defined as <1 g/L).

Table 4. Characteristics of women with connective tissue disease and silicone breast implants who were previously diagnosed with paraproteinemia (Group 6). Subjects are listed in increasing order of age.*

Age (yrs)	Connective tissue disease		Silicone implant				Serum paraprotein** (Concentration and isotype)
	Type	Duration (yrs)	Type	Duration (yrs)	Exposure (yrs)	Rupture***	
43	UCTD/FMS	7.0	silicone gel	14.2	17.1	yes	6 g/L IgG(κ)
44	UCTD	12.8	silicone gel	15.3	17.7	no	3 g/L IgG(λ), 3 g/L IgG(λ)
46	UCTD	7.1	silicone gel	15.1	17.2	yes	4 g/L IgG(κ), IgG(λ)
50	UCTD	4.0	silicone gel/polyurethane	10.5	17.4	yes	5 g/L IgM(κ)
50	UCTD	8.0	silicone gel	n/a	19.2	yes	13 g/L IgG(κ), 6 g/L IgG(κ)
52	UCTD	4.6	silicone gel	14.1	20.5	yes	4 g/L IgG(κ)
54	UCTD	3.0	silicone gel/saline	11.4	14.2	yes	1 g/L IgG(κ)
55	UCTD/FMS	5.0	silicone gel	21.0	30.0	yes	7 g/L IgG(λ)
56	UCTD	10.4	silicone gel	15.1	23.3	no	9 g/L IgG(κ)
58	UCTD	9.3	silicone gel	13.5	18.1	yes	22 g/L IgG(λ)
All: 50.8 ± 5.2		7.1 ± 3.1			14.5 ± 3.0	19.5 ± 4.4	

Footnotes to Table 4:

Abbreviations per Tables 1 and 2

* All subjects were White.

** Weak paraprotein bands (defined as <1 g/L) are shown without specifying their concentration; all others are shown by concentrations estimated from protein electrophoresis.

*** Implant rupture was suspected by signs and symptoms in eight cases and documented at surgery in five cases

Figure 1

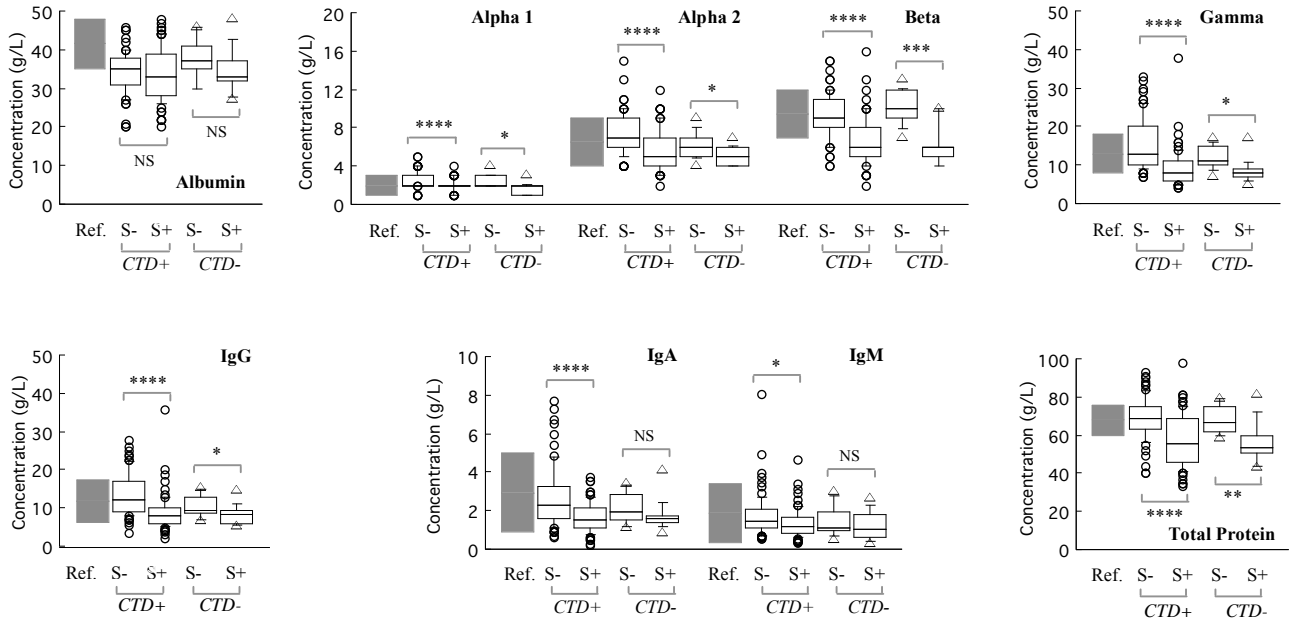
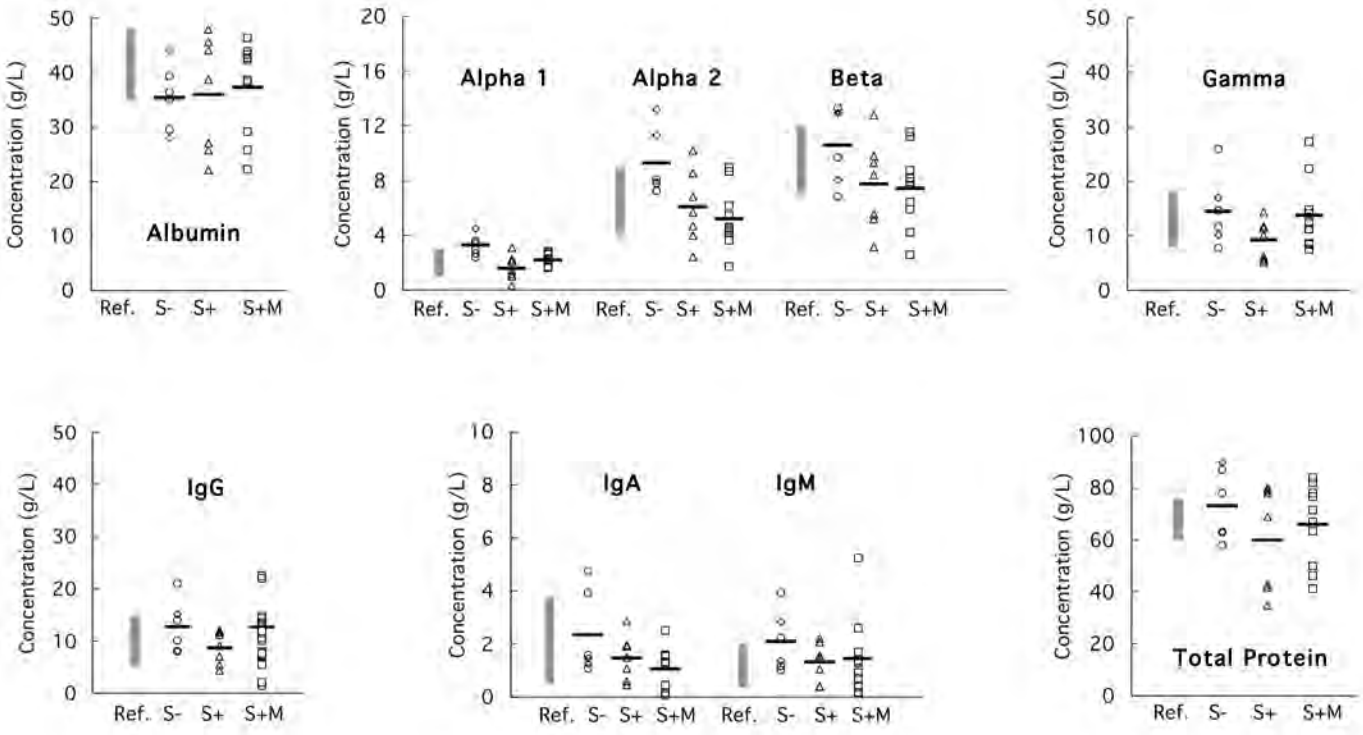

Albumin
Alpha 1
Alpha 2
Beta
Gamma
IgG
IgA
IgM
Total Protein
Concentration (g/L)
Ref.
S-
S+
CTD+
CTD-
NS
****
***
**
*

Figure 2


Albumin
Alpha 1
Alpha 2
Beta
Gamma
IgG
IgA
IgM
Total Protein
Concentration (g/L)
Ref.
S-
S+
S+M

Available online at www.sciencedirect.com
ScienceDirect
European Journal of Pain 11 (2007) 202–207
www.EuropeanJournalPain.com

The association between experimental and clinical pain measures among persons with fibromyalgia and chronic fatigue syndrome

Michael E. Geisser [a,b,*], Richard H. Gracely [a], Thorsten Giesecke [c], Frank W. Petzke [c], David A. Williams [a], Daniel J. Clauw [a]

[a] *Chronic Pain and Fatigue Research Center, Department of Internal Medicine, Division of Rheumatology, University of Michigan, Ann Arbor, MI, United States*
[b] *Department of Physical Medicine and Rehabilitation, University of Michigan Health System, 325 E. Eisenhower Parkway, Ann Arbor, MI 48108, United States*
[c] *Department of Anesthesiology and Intensive Care, University of Cologne, Cologne, Germany*

Received 5 October 2005; received in revised form 30 January 2006; accepted 5 February 2006
Available online 20 March 2006

Abstract

Evoked or experimental pain is often used as a model for the study of clinical pain, yet there are little data regarding the relationship between the two. In addition, there are few data regarding the types of stimuli and stimulus intensities that are most closely related to clinical pain.

In this study, 36 subjects with fibromyalgia (FM), chronic fatigue syndrome (CFS), or both syndromes were administered measures of clinical pain and underwent a dolorimetry evaluation. Subjects also underwent experimental pain testing utilizing heat and pressure stimulation. Stimulation levels evoking low, moderate and high sensory intensity, and comparable levels of unpleasantness, were determined for both types of stimuli using random staircase methods. Clinical pain was assessed using visual analogue ratings and the short form of the McGill Pain Questionnaire (MPQ).

Ratings of heat pain sensation were not significantly associated with clinical pain ratings, with the exception of unpleasantness ratings at high stimulus intensities. Pain threshold and tolerance as assessed by dolorimetry were significantly associated with average measures of clinical pain. Both intensity and unpleasantness ratings of pressure delivered using random staircase methods were significantly associated with clinical pain at low, moderate and high levels, and the strength of the association was greater at increasingly noxious stimulus intensities.

These findings suggest that random pressure stimulation as an experimental pain model in these populations more closely reflects the clinical pain for these conditions. These findings merit consideration when designing experimental studies of clinical pain associated with FM and CFS.

Keywords: Fibromyalgia; Chronic fatigue syndrome; Chronic pain; Experimental pain

1. Introduction

Experimental studies designed to deliver noxious stimuli to subjects under controlled conditions are frequently used to make inferences about clinical pain conditions. Despite this, little is known about the

* Corresponding author. Tel.: +1 734 763 6501; fax: +1 734 936 7048.
E-mail address: mgeisser@med.umich.edu (M.E. Geisser).

1090-3801/$32
doi:10.1016/j.ejpain.2006.02.001

relationship between experimental pain perception and clinical pain, and there is a lack of research on the experimental methods and types of stimuli that are most highly associated with clinical pain (Gracely, 1999). Such studies are highly important as evoked pain is increasingly being used to study central nervous system (CNS) abnormalities associated with clinical pain conditions such as fibromyalgia (FM), temporomandibular disorders, vulvodynia, and other entities (Geisser et al., 2003; Giesecke et al., 2004; Diatchenko et al., 2005; Petzke et al., 2003a). While pain is not a central feature of chronic fatigue syndrome (CFS), five of eight minor criteria (of which four are necessary to make the diagnosis) for CFS are pain-based (Fukuda et al., 1994). Common CNS abnormalities have been proposed to underlie all of these disorders (Clauw and Chrousos, 1997), and determining the experimental methods that best reproduce the clinical abnormalities associated with these conditions is crucial to their study.

Previous research has shown that persons with FM display heightened responsiveness to auditory tones (McDermid et al., 1996), contact thermal heat in both the noxious and innocuous ranges (Geisser et al., 2003; Kosek et al., 1996; Kosek and Hansson, 1997; Lautenbacher et al., 1994; Staud et al., 2001), ischemic pain (Kosek and Hansson, 1997), pressure applied to the thumb (Gracely et al., 2002; Petzke et al., 2003a) and electrical stimulation (Lautenbacher et al., 1994). Differences between FM subjects and controls have also been observed using methodologies that stimulate abnormal temporal summation of pain or wind-up (Staud et al., 2001, 2003) and the regulation of diffuse noxious inhibitory controls (Kosek and Hansson, 1997). However, only a few studies have examined how these abnormalities relate to the experience of clinical pain. Lautenbacher et al. (1994) reported low associations between measures of clinical pain and responses to electrocutaneous stimuli, pressure and heat. The authors also found that pressure pain thresholds at two sites were significantly associated with clinical pain. Staud et al. (2003) found that a combination of variables including measures of wind-up, pain-related negative affect, and tender point counts accounted for 49% of the variance in clinical pain. Further research is needed to determine the types of stimuli and experimental methods that are most highly associated with clinical pain states. In addition, previous research suggests that experimental methods that employ gradually ascending stimulation are more highly associated with psychological factors that may bias pain ratings (Petzke et al., 2003).

In the present study, we examined the relationships between clinical pain and a variety of evoked pain measures including gradually ascending pressure (dolorimetry) and a random staircase method of stimulus presentation of both pressure and heat stimuli. Based on prior research, we hypothesized that the random staircase methods would be more highly associated with measures of clinical pain compared to dolorimetry. In addition, we hypothesized that pressure pain perception would be more highly associated with measures of clinical pain compared to heat pain perception, as previous research has suggested that pressure sensitivity is highly associated with musculoskeletal pain syndromes (Diatchenko et al., 2005; Rollman and Lautenbacher, 2001). Since both momentary and average clinical pain were assessed, we also examined whether evoked pain was more highly associated with patients' usual pain, or more highly correlated with pain at the time of testing.

2. Materials and methods

2.1. Subjects

Thirty-six subjects who met either the 1990 American College of Rheumatology criteria for fibromyalgia (FM) (Wolfe et al., 1990), the diagnostic criteria for chronic fatigue syndrome (CFS) (Fukuda et al., 1994), or both diagnoses, were included in the study. Subjects with CFS had to have at least one pain symptom to be eligible. Eight subjects were diagnosed with FM alone, eight with CFS alone, and 20 fulfilled the diagnostic criteria for both disorders. Twenty-seven were female, and nine were male. Twenty-three were Caucasian, six were African-American, two were Hispanic, two were Asian-American, and three were of other descent. The mean age was 39.6 (SD = 9.2) years. Mean duration of pain was 96.5 months (SD = 80.9). Subjects with psychiatric disorders that did not interfere with study participation were not excluded.

The study was approved by the Georgetown University Medical Center's institutional review board, and informed consent was obtained from all participants for study on the General Clinical Research Center. All patients underwent a comprehensive screening during which the diagnosis was confirmed and co-morbidities were evaluated. Exclusion criteria were severe physical impairment, medical conditions that were capable of causing patients' symptoms (e.g., morbid obesity, autoimmune/inflammatory diseases, cardiopulmonary disorders), uncontrolled endocrine or allergic disorders (i.e., hyper-/hypothyroidism, diabetes, allergic rhinitis), malignancy, severe psychiatric illnesses (e.g., schizophrenia, substance abuse), factors known to affect the hypothalamic pituitary axis (HPA) or autonomic function (e.g., cigarette smoking, daily intake of caffeine exceeding the equivalence of two cups of coffee), or medication usage other than as-needed analgesics (excluding long-term narcotics). We did not exclude subjects with psychiatric conditions that are associated with HPA dysfunction (e.g., major depression). Eleven subjects who fulfilled the diagnostic criteria were excluded as

these subjects did not complete all of the study measures examined in the current manuscript.

Subjects who qualified for inclusion in the study were scheduled for a 2-day study protocol. They were asked to discontinue intake of antidepressants up to four weeks ahead of the appointment (depending on the drug), but were allowed to use non-steroidal anti-inflammatory drugs until three days before the appointment. On the first day of the study, patients completed the self-report questionnaires and were familiarized with the pain testing paradigm. On the following day, they participated in a pain psychophysical testing session.

2.2. Measures

2.2.1. Clinical pain

Clinical pain was assessed using the short-form of the McGill Pain Questionnaire (MPQ; Melzack, 1987). This questionnaire contains 15 pain adjectives, and a total score is obtained by summing responses to all the items. The present pain intensity (PPI) subscale was examined as an indicator of pain intensity at the time of testing. The scale is sensitive to change produced by various pain interventions, and is highly correlated with the parent scale (Melzack, 1987).

Self-report of clinical pain intensity was also obtained by visual analogue scale (VAS) ratings. The scale was 100 mm long and anchored by the statements ''no pain'' on the left and ''the most intense pain imaginable'' on the right. Separate VAS scales were used to measure subjects' level of pain on the day of testing and average pain over the past month. VAS ratings have demonstrated good reliability (Boeckstyns and Backer, 1989; Revill et al., 1976) and concurrent validity when compared to other methods of pain measurement (Downie et al., 1978; Jensen et al., 1989).

2.2.2. Pressure and heat pain assessment

Evoked pain was assessed for both pressure and heat stimuli. Pressure pain sensitivity was evaluated by subjective scaling of pain sensations evoked by discrete 5-s pressure stimuli applied to the fixated left thumbnail with a 1-cm^2 hard rubber probe. Previous studies have shown that ''neutral'' regions, such as the thumb, accurately reflect an individual's overall pressure pain sensitivity (Petzke et al., 2001). The rubber probe was attached to a hydraulic piston, which was connected via a combination of valves to a second piston. Application of calibrated weights to the second piston produced controlled, repeatable pressure pain stimuli of rectangular waveform, that is, subjects experienced no pressure, then the target stimulus pressure when the appropriate weight was placed on the second piston. Subjects rated the intensity and unpleasantness dimensions of pressure pain sensations using a combined numerical (0–20) analog descriptor scale (Gracely et al., 1979). For each dimension, a series of 5-s stimuli were delivered to the right thumbnail in ascending order in 0.5 kg of force per square centimeter (kg/cm^2) increments after an initial stimulus of 0.25 kg/cm^2, up to a maximum of 10 kg/cm^2. A second series of pressure stimuli was administered using the multiple random staircase (MRS) method (Gracely et al., 1988). A software system uses the data collected from the ascending series to compute starting stimulus intensities for another set of stimuli controlled by the method of MRS's. The MRS is an interactive system in which the software logic continuously adjusts the stimulus intensity to maintain ratings at several specific levels. In this implementation, three independent staircases are titrated to produce pain sensations rated between 0 and 1 (no sensation to faint pain), between 9 and 10 (mild–moderate pain), and between 13 and 14 (strong–slightly intense pain) on the 0–20 box scale. In the remainder of this report, these levels are referred to as low, medium, and high. On each trial, the method randomly selects a staircase and delivers the stimulus intensity associated with that staircase. The response determines the next stimulus delivered by that staircase the next time it is selected. This determination is based on the previous response history and uses a dynamically changing step size to estimate the stimulus intensity required to produce the level of pain associated with each particular staircase. The method will deliver 12 stimuli for each of the three staircases, for a total of 36 stimuli delivered over 12 min. If any staircase has not converged after 12 stimuli, the operator will be able to continue the method until convergence is reached or until 72 total stimuli have been delivered.

Heat pain sensations were evoked by a 1 cm diameter contact thermode system. A low-mass electrical heater on a water-perfused cold sink with feedback circuitry delivered precise stimulus waveforms with a ramp rate of 10 °C/s. The thermal stimuli were delivered to the volar surface of the non-IV forearm. As with the pressure testing, both an ascending and a multiple random staircase series of thermal stimuli were presented to each subject. The temperatures required to evoke ratings of low, medium, and high pain intensity and unpleasantness were calculated for each subject.

2.2.3. Dolorimetry

A dolorimeter with a 1 cm^2 tip was used to determine pain threshold and tolerance levels bilaterally at the thumb and lateral epicondyle. Pressure was increased at a rate of 1 kg/cm^2 per second and subjects were instructed to indicate when they first perceived pain (threshold) and when the pain became unbearable (tolerance). Pressure was stopped once the pain became unbearable or if 12 kg/cm^2 of pressure was reached. These sites were chosen as previous research has shown that these points are highly correlated with overall tenderness (Petzke et al., 2001). The measures from each

side of the body were averaged to produce one value for each stimulus site.

3. Results

Table 1 shows the means and standard deviations for pressure and thermal intensities needed to evoke sensations of mild, medium, and high sensory intensity and unpleasantness using the random staircase procedure, and displays the threshold and tolerance averages for dolorimetry measured at the thumb and lateral epicondyle.

An initial analysis examined whether the patient groups differed on any of the clinical or experimental pain measures. Oneway analysis of variance (ANOVA) revealed that the groups significantly differed on VAS ratings of pain today ($F = 7.0$, $p = .003$) and pain over the past month ($F = 4.1$, $p = .03$). Post hoc tests (Duncan) indicated that subjects diagnosed with both FM and CFS had higher ratings of pain today compared to the other two groups, and had higher VAS ratings of pain over the past month compared to subjects diagnosed with CFS alone. In addition, the groups significantly differed on pain threshold ($F = 3.2$, $p = .05$) and tolerance ($F = 3.2$, $p = .05$) assessed by dolorimetry at the lateral epicondyle. Post hoc tests revealed that subjects with CFS alone had significantly higher pain threshold and tolerances compared to subjects with both CFS and FM.

Correlations between the clinical pain measures, dolorimetry, and heat and pressure pain measures (stimulus intensities needed to evoke different levels of pain sensation) are presented in Table 2. The correlations indicate that pressure stimuli delivered using the random staircase method were significantly associated with ratings on the MPQ for both unpleasantness and intensity at all stimulus levels, with the exception of low unpleasantness ratings. In addition, pressure stimuli at high levels of intensity and unpleasantness were significantly associated with VAS ratings of pain over the past month. The magnitude of this association became greater as the stimulus intensity increased. Measures of pain threshold and tolerance assessed by dolorimetry at the lateral epicondle were significantly and inversely related to the MPQ total score and average VAS over the past month, indicating lower pain thresholds and tolerance were significantly associated with higher clinical pain. Pain thresholds and tolerances measured at the thumb using dolorimetry were not significantly associated with these same measures. None of the dolorimetry, heat or pressure pain measures were significantly correlated with measures of pain assessed on the day of testing.

Measures of heat pain sensitivity delivered using the random staircase procedure were not significantly associated with clinical pain ratings, with the exception of high unpleasantness ratings and McGill total pain scores and VAS ratings of pain over the past month.

To determine whether the significant correlations obtained between the experimental and clinical pain measures significantly differed across experimental methods, the formula for comparing two correlation coefficients from related samples was utilized (Weinberg and Goldberg, 1979, p. 412). Comparing the associations between intensity and unpleasantness levels and clinical pain assessed by the MPQ utilizing the MRS pressure method versus heat, the associations with

Table 1
Means (SD) of experimental heat and pressure measures

Measure	Mean (SD)
Lateral epicondyle threshold (kg/cm^2)	5.4 (2.5)
Lateral epicondyle tolerance (kg/cm^2)	7.2 (3.0)
Thumb threshold (kg/cm^2)	6.6 (3.0)
Thumb tolerance (kg/cm^2)	8.2 (3.1)
Low pressure intensity (kg/cm^2)	2.3 (1.8)
Medium pressure intensity (kg/cm^2)	4.7 (2.5)
High pressure intensity (kg/cm^2)	6.5 (2.7)
Low pressure unpleasantness (kg/cm^2)	2.7 (2.3)
Medium pressure unpleasantness (kg/cm^2)	5.4 (2.7)
High pressure unpleasantness (kg/cm^2)	7.4 (2.9)
Low heat intensity (°C)	38.3 (2.8)
Medium heat intensity (°C)	43.0 (4.1)
High heat intensity (°C)	46.9 (4.5)
Low heat unpleasantness (°C)	39.3 (3.6)
Medium heat unpleasantness (°C)	44.9 (4.8)
High heat unpleasantness (°C)	48.2 (4.5)

Table 2
Correlations between experimental and clinical pain measures

Measure	McGill total	VAS past month	PPI	VAS today
Dolorimeter				
Lateral epicondyle threshold	−.36*	−.34*	−.17	−.23
Lateral epicondyle tolerance	−.41*	−.35*	−.24	−.30
Thumb threshold	−.22	−.16	−.09	−.11
Thumb tolerance	−.31	−.25	−.20	−.24
Pressure				
Low intensity	−.42*	−.21	−.18	−.23
Medium intensity	−.48*	−.23	−.22	−.24
High intensity	−.52*	−.33*	−.27	−.27
Low unpleasantness	−.30	.00	−.13	−.10
Medium unpleasantness	−.45*	−.19	−.22	−.16
High unpleasantness	−.52*	−.35*	−.27	−.22
Heat				
Low intensity	−.14	−.18	.06	−.11
Medium intensity	−.20	−.31	.02	−.17
High intensity	−.24	−.31	−.03	−.15
Low unpleasantness	−.10	−.07	.03	.00
Medium unpleasantness	−.20	−.24	.01	−.08
High unpleasantness	−.36*	−.35*	−.15	−.17

* $p < .05$.

MRS pressure were significantly higher for the medium ($t = -2.3$, $p = .03$) and high ($t = -2.8$, $p = .01$) intensity stimuli compared to the same levels obtained using MRS heat. A similar result was also obtained for medium ($t = -2.1$, $p = .05$) unpleasantness stimuli. When VAS ratings of pain during the past month were examined, the associations between this measure and stimulation levels obtained using MRS heat and MRS pressure did not differ. The correlations between dolorimetry and clinical pain did not significantly differ from those observed between MRS heat or pressure and clinical pain. The magnitude of the associations between MRS pressure and clinical pain, and dolorimetry and clinical pain, were also not significantly different.

As trends were evident suggesting that higher stimulation levels were more strongly associated with clinical pain compared to less intense levels, these correlations were also compared using the same method noted above. For dolorimetry, associations between dolorimetry and clinical pain comparing the threshold and tolerance measures did not significantly differ. For MRS pressure and heat, the associations across different intensity rating levels also were not significantly different. For unpleasantness ratings, the association between pressure high unpleasantness and VAS ratings of pain over the past month was significantly greater than the association between pressure low unpleasantness and this same measure of clinical pain ($t = -2.8$, $p = .01$). Also, the difference in the associations between pressure low unpleasantness and MPQ scores and high pressure unpleasantness and MPQ scores approached significance ($t - 1.8$, $p = .08$).

4. Discussion

Pain sensitivity determined by pressure stimulation using the multiple random staircase (MRS) procedure was significantly and inversely associated with average measures of clinical pain intensity, while heat was not. Comparing the magnitude of the associations, the correlations between MRS measures of pressure and clinical pain as assessed by the MPQ were significantly higher than those obtained between MRS heat and clinical pain. None of the experimental pain measures were significantly associated with measures of clinical pain assessed at the time of testing. These findings suggest that responses to evoked pressure pain in patients with FM and CFS can be generalized to patients' overall clinical condition, and that fluctuations in clinical pain that may occur during psychophysical testing do not significantly influence evoked pain responses. These findings also suggest that pressure stimulation as an experimental pain model among subjects with FM and CFS more closely reflects the average clinical pain associated with these conditions, and is consistent with other research suggesting that mechanical stimulation is an especially sensitive measure for the analysis of pathology associated with musculoskeletal pain (Diatchenko et al., 2005; Rollman and Lautenbacher, 2001).

In general, ratings given to higher stimulus intensities were more strongly associated with average ratings of clinical pain. These findings highlight the importance of evoked pain studies and provide further justification for the use of suprathreshold stimuli in experimental pain paradigms. The findings also suggest that experimental application of innocuous stimuli as a model for clinical pain may not be as generalizable to clinical pain conditions. In addition, the findings suggest that methods used to assess pain thresholds may not be as generalizable to clinical pain compared to studies employing suprathreshold methods of pain stimulation. This conclusion needs to be interpreted cautiously as significantly higher correlations between higher levels of experimental pain stimulation and clinical pain were only obtained for unpleasantness ratings and not intensity ratings, and this finding was only evident using the MRS pressure stimulation method. Further research examining the risk/benefit of noxious stimulus intensities in relation to the generalizability of the findings and subject burden would be beneficial.

Pressure stimulation using both dolorimetry and random staircase methods were both significantly associated with average measures of clinical pain. However, our previous research suggests that random staircase methods are less prone to biases associated with gradually ascending stimuli, and therefore are less likely to be influenced by affective states that frequently accompany pain, such as depression. In the present study, the magnitude of the associations between random staircase measures of pressure sensation and clinical pain as assessed by the McGill were somewhat higher than they were for dolorimetry, although this difference was not statistically significant. Further research is needed to determine the types of evoked pain models that most closely reflect the mechanisms underlying different clinical pain conditions.

It should be noted that the design of the present study is cross-sectional, and therefore no inferences can be made about causality. In addition, this study only examined a few of the experimental pain paradigms published in the literature, and therefore the findings cannot speak to the generalizability of other experimental methods to clinical pain, such as electrical stimulation. Third, the study examined patients with pain associated with FM and CFS, and the findings may not be generalizable to other clinical pain conditions. Fourth, this study examined the correlation between clinical pain intensity and experimental pain perception, and did not examine the ability of experimental methods to discriminate between persons with and without chronic pain. Such a comparison would also be beneficial in examining the validity of various methods of experimental pain.

Acknowledgements

Funding for this study came in part from Department of the Army Grant DAMD-17002-0018 and Grant M01 RR-13297 from the National Center for Research Resources, National Institutes of Health.

References

Boeckstyns MEH, Backer M. Reliability and validity of the evaluation of pain in patients with total knee replacement. Pain 1989;38:29–33.

Clauw DJ, Chrousos GP. Chronic pain and fatigue syndromes:overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. Neuroimmunomodulation 1997;4:134–53.

Diatchenko L, Slade GD, Nackley AG, Bhalang K, Sigurdsson A, Belfer I, et al. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Human Molecular Genetics 2005;14:135–43.

Downie WW, Leatham PA, Rhind VM, Wright V, Branco JA, Anderson JA. Studies with pain rating scales. Ann Rheum Dis 1978;37:378–81.

Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A The International Chronic Fatigue Syndrome Study Group. The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med 1994;121:953–9.

Geisser ME, Casey KL, Brucksch CB, Ribbens CM, Appleton BB, Crofford LJ. Perception of noxious and innocuous heat stimulation among healthy women and women with fibromyalgia:association with mood, somatic focus, and catastrophizing. Pain 2003;102:243–50.

Giesecke J, Reed BD, Haefner HK, Giesecke T, Clauw DJ, Gracely RH. Quantitative sensory testing in vulvodynia patients and increased peripheral pressure pain sensitivity. Obstetrics & Gynecology 2004;104:126–33.

Gracely RH. Studies of pain in human subjects. In: Wall PD, Melzack R, editors. Textbook of pain. New York: Churchill Livingstone; 1999. p. 385–407.

Gracely RH, Dubner R, McGrath PA. Narcotic analgesia: fentanyl reduces the intensity but not the unpleasantness of painful tooth pulp sensations. Science 1979;203:1261–3.

Gracely RH, Lota L, Walter DJ, Dubner R. A multiple random staircase method of psychophysical pain assessment. Pain 1988;32:55–63.

Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 2002;46:1333–43.

Jensen MP, Karoly P, O'Riordan EF, Bland Jr F, Burns RS. The subjective experience of acute pain: an assessment of the utility of 10 indices. Clin J Pain 1989;5:153–9.

Kosek E, Eckholm J, Hansson P. Sensory dysfunction in fibromyalgia patients with implications for pathogenic mechanisms. Pain 1996;68:375–83.

Kosek E, Hansson P. Modulatory influence on somatosensory perception from vibration and heterotopic noxious conditioning (HNCS) fibromyalgia patients and healthy subjects. Pain 1997;70:41–51.

Lautenbacher S, Rollman GB, McCain GA. Multi-method assessment of experimental and clinical pain in patients with fibromyalgia. Pain 1994;59:45–53.

McDermid AJ, Rollman GB, McCain GA. Generalized hypervigilance in fibromyalgia: Evidence of perceptual amplification. Pain 1996;66:133–44.

Melzack R. The short-form McGill Pain Questionnaire. Pain 1987;30:191–7.

Petzke F, Khine A, Williams D, et al. Dolorimetry performed at 3 paired tender points highly predicts overall tenderness. J Rheumatol 2001;28:2568–9.

Petzke F, Clauw DJ, Ambrose K, Khine A, Gracely RH. Increased pain sensitivity in fibromyalgia: effects of stimulus type and mode of presentation. Pain 2003;105:403–13.

Petzke F, Gracely RH, Park KM, Ambrose K, Clauw DJ. What do tender points measure? Influence of distress on 4 measures of tenderness. J Rheum 2003;30:567–74.

Revill SI, Robinson JO, Rosen M, Hogg MIJ. The reliability of a linear analogue for evaluating pain. Anesthesia 1976;31:1191–8.

Rollman GB, Lautenbacher S. Sex differences in musculoskeletal pain. Clin J Pain 2001;17:20–4.

Staud R, Vierck CJ, Cannon RL, Mauderli AP, Price DD. Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. Pain 2001;91:165–75.

Staud R, Cannon RC, Mauderli AP, Robinson ME, Price DD, Vierck Jr CJ. Temporal summation of pain from mechanical stimulation of muscle tissue in normal controls and subjects with fibromyalgia syndrome. Pain 2003;102:87–95.

Weinberg SL, Goldberg KP. Basic statistics for education and the behavioral sciences. Boston, MA: Houghton Mifflin Company; 1979.

Wolfe FW, Smythe HA, Yunas MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Arthritis Rheum 1990;33:160–72.

Available online at www.sciencedirect.com
ScienceDirect
Pulmonary Pharmacology & Therapeutics 20 (2007) 433–437
PULMONARY PHARMACOLOGY & THERAPEUTICS
www.elsevier.com/locate/ypupt

Cough, pain and dyspnoea: Similarities and differences

Richard H. Gracely[a], Bradley J. Undem[b], Robert B. Banzett[c,*]

[a]*Departments of Medicine-Rheumatology and Neurology, University of Michigan Health System, VA Ann Arbor Healthcare System, Ann Arbor, MI 48106, USA*
[b]*Johns Hopkins School of Medicine, Johns Hopkins Asthma Center, Baltimore, MD 21224, USA*
[c]*Harvard Medical School, Department of Medicine, Division of Pulmonary and Critical Care Medicine, Beth Israel Deaconess Medical Center, Boston, MA 02215, USA*

Received 13 December 2006; accepted 20 December 2006

Abstract

The three common symptoms, pain, dyspnoea and cough, share some important features. We felt that the analogies to be made among them could be instructive, possibly suggesting new avenues of research. Each of these symptoms can be profoundly uncomfortable, and can profoundly degrade quality of life. The sign, cough, is often given more prominence than the symptom, urge to cough, but both are important to the patient (the former may be of more concern to nearby people). Advances in pain research over the last several decades have pointed the way to new studies of dyspnoea; they may serve as a model for the psychophysical study of the perception of urge to cough, as well as providing models for understanding both central and peripheral sensitization of the afferent pathway. We briefly review here the afferent and central pathways and psychophysics of pain, dyspnoea and urge to cough.

Keywords: Cough; Pain; Dyspnoea; Urge to cough; Referred pain; Psychophysics

1. Introduction

Pain, dyspnoea and cough are very common and troubling symptoms. There are a number of important analogies to be made among these three common symptoms (internal sensations). Each of these symptoms can be profoundly uncomfortable. All three of these symptoms also produce externally observable signs—this is most prominent in the case of cough, where the sign, cough, is often given more prominence than the symptom, urge to cough. This may be true because cough is more easily quantified than urge to cough, or because cough is more disturbing to surrounding people (e.g. in a concert hall) than are withdrawal from pain or laboured breathing. In all cases, we must ask what is it we wish to treat, sign or symptom—what is important to the patient? In all cases, treatment to the extent of eliminating the symptom entirely may put the patient at risk, while inadequate treatment may allow a profound decrease in quality of life and ability to work.

The rapid, near explosive growth in pain research serves as both a scientific and political model for future advances in cough and dyspnoea. The advances in pain research are the result of tireless efforts from a number of individuals, exemplified by the late John Bonica, who worked vigorously at all levels of scientific organization, business, government and the press to advance the quality and quantity of pain research and treatment. As a result, our knowledge of pain has grown dramatically. In the early 1970s, the entire field of pain, like the current fields of cough and dyspnoea, received only a brief mention, if any, in typical medical textbooks. The field of pain research has grown so rapidly that now no one person can grasp all of it; the latest Textbook of Pain condenses it into 1214 pages! This advance in pain research serves as an excellent social–political model, and also as an excellent scientific model that may share many features with cough and dyspnoea. We describe here the physical and experiential similarities of these three disorders with the view to suggesting future research directions.

*Corresponding author.
E-mail addresses: rgracely@med.umich.edu (R.H. Gracely), Dyspnea@HSPH.harvard.edu (R.B. Banzett).

1094-5539/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.pupt.2006.12.005

2. Afferent inputs

Pain, cough and dyspnoea share a common feature: they originate in afferent nervous systems that detect and signal real or impending threats to the organism.

2.1. Affferent nerves and pain

Pain sensations are mediated by a family of nociceptor afferents that can be divided into relatively fast conducting, thinly myelinated A-δ nociceptors and the slower conducting, nonmyelinated C-fibre nociceptors. The evoked sensations are distinct. A-δ nociceptors mediate sensations of pricking mechanical or thermal pain and cold pain that usually are easily localized. In contrast, C-fibres usually mediate sensations of burning heat or deep pressure that are diffuse and poorly localized [1]. Neuropeptides are typically limited to a subset of C-fibre neurones. Both types of pain fibres from the majority of somatic structures enter the dorsal horn of the spinal cord but synapse at different locations.

Pain afferent systems are not static. Injury, inflammation or repeated stimulation can sensitize the pain system at both the peripheral level of nociceptors and at spinal and higher levels [1]. Intrinsic systems that exacerbate pain serve a recuperative function, assisting healing by promoting behaviours that immobilize and protect an injured area. The cough system may also be sensitized at the peripheral and central level. This sensitization may serve an equally important biological function: for instance, healing can be promoted by voluntary pain-related behaviours. However, there are many instances in which excessive or prolonged pain or cough sensitivity seems to serve little purpose, and may even interfere with healing. Such inappropriate sensations are likely targets of therapeutic interventions. For pain, such interventions are usually termed analgesics and include both peripheral and centrally acting agents as well as non-pharmacological interventions. Opioid agents such as morphine are classic analgesics that can be effective for pain, cough and dyspnoea. Opiates, however, are not always effective, and have well-known deleterious effects. Specific interventions can also reduce pain by an additional mechanism. Reducing inflammation or muscle spasm, or inhibiting migraine headaches, is not accomplished by an analgesic attenuation of afferent input. Rather, it is caused by reducing the physical conditions that sensitize or activate the afferent system. This mechanism, which lacks a specific term in pain control, may play a more significant role in cough and dyspnoea.

2.2. Afferent nerves and cough

At the level of the primary afferent nerves, pain and cough pathways are remarkably analogous. Sensations such as referred pain and allodynia also find similarities in various cough disorders. As with pain, cough can be evoked in experimental animals by stimulation of nociceptive C-fibres as well as by faster conducting Aδ-fibres [2]. The majority of cough afferents travel in the vagus nerve. Just as the quality of painful sensations may depend on whether C-fibres or Aδ-fibres are activated, it is likely that the quality of the sensation of the urge to cough depends on the type of afferent nerve being stimulated. For example, the violent immediate cough evoked by spritzing tartaric acid on the human larynx is likely due to stimulation of Aδ-fibres [3]. In guinea pigs, Aδ-fibres that evoke cough are strongly activated by acidic solutions and are situated in the larynx, trachea and main bronchi. These fibres do not respond to chemicals that stimulate C-fibres such as capsaicin and bradykinin. The cough-evoking Aδ-fibers in large airways respond to punctate mechanical stimulation, anosmotic solutions and acids [2]. In some studies, these Aδ-fibres that can lead to cough are referred to as ''irritant receptors''. Cough evoked by the Aδ-fires in the large airways can be evoked even in anaesthetized animals [4].

Several stimulants known to selectively stimulate nociceptive C-fibres but not A fibres in the airways (e.g. capsaicin, bradykinin) also evoke cough in laboratory animals and humans [5]. Inflammatory conditions can lead to changes in their electrical excitability as well phenotypic changes caused by changes in gene transcription rates [6]. The C-fibre-evoked cough, however, is very sensitive to general anaesthesia, and low levels of the C-fibre stimulation evoke urge to cough sensations that are similar to an irritating itch.

2.2.1. Referred pain and referred cough

It has long been known that pain can be perceived at sites distant from the site of injury and afferent nerve stimulation. This phenomenon is termed referred pain. This is especially common with visceral pain disorders [7]. In these cases it is hypothesized that the visceral nociceptive nerves converge on dorsal horn neurones that also receive specific somatosensory input from other sites in the body. For example, a nociceptive fibre in the heart may interact with neurones in the dorsal horn that are normally involved with conveying painful sensations in the left arm. When these cardiac C-fibres are stimulated by inflammation or hypoxia, transmitters are released from the central terminals at these synapses such that pain is now diffusely sensed in the left arm.

2.2.2. Central sensitization

Like the primary afferent nerves involved in pain, the vagal C-fibres and cough-evoking tracheal Aδ-fibres are not static. The transmitters released from converging nociceptors may also lead to long-lasting changes in the secondary neurones leading to a synaptic sensitization (''central sensitization'') [8]. This can lead to pain being evoked even by an ordinarily non-painful stimulus, such as lightly brushing the arm; this phenomenon is termed allodynia. Among the mechanisms that may underlie allodynia is central sensitization of afferent pain pathways

caused by converging nociceptor input; this has been well described in many experimental systems [9,10].

It now appears that there is a similar convergence of nociceptive vagal C-fibre afferent nerves onto secondary neurones involved in cough [11]. Moreover, even in the absence of convergence in the strict sense, the peptides released from the vagal C-fibres (e.g. neurokinins and calcitonin gene-related peptide) may modulate the efficacy of large numbers of nearby synapses. This could lead to conditions where C-fibre stimulation sensitizes the cough pathways to the extent that even non-tussive stimuli evoke urge to cough sensations analogous to allodynia. This could also lead to ''referred cough'' sensations analogous to the referred pain discussed above. Mechanically probing the larynx, trachea or large bronchi causes an immediate and violent cough. By contrast, mechanically probing the lungs, nose or oesophagus does not evoke cough. Stimulating nociceptors in the lungs or oesophagus can, however, lead to cough [12,13], and in humans oesophageal reflux is one of the most common causes of chronic cough [14]. A likely explanation is the process of central sensitization. In other words, stimulating C-fibre terminals in the oesophagus (or lungs) causes the release of transmitters and peptides in the brainstem that then sensitize the cough reflex pathway originating in the laryngeal and tracheal receptors [12]. If this is the case, one might suspect that inflammation in the lungs or oesophagus could lead to referred sensations of irritation in the throat. Try as one might to clear the throat or scratch that itch, the sensation rapidly returns. Why? We suggest that it is because the seat of the problem is elsewhere, and the sensation is referred from the distant site. The cough evoked by stimulating the wall of the external acoustic meatus of the ear (Arnold's reflex) may be another example of a referred cough reflex [15]. By analogy, the photic-sneeze reflex is an example in which the optic sensory nerve stimulation somehow leads to nasal urge to sneeze sensations, presumably by centrally sensitizing the nasal trigeminal sneeze pathway [16].

2.3. *Afferent nerves and dyspnoea*

The afferent pathways for dyspnoea are more complex, reflecting the fact that there are actually several different uncomfortable breathing sensations that are classed as dyspnoea [reviewed in 17,18]. These sensations can be varied separately, and have different afferent pathways [e.g. 19,20]. The sense of excessive respiratory work is thought to arise both from receptors in the respiratory pump muscles themselves, and from awareness of cortical motor drive sent to the pump muscles [e.g. 21,22]. The sense of air hunger is thought to arise from any reflex drive to breathe, such as arterial chemoreceptors sensing hypercapnia and hypoxia [23]; the pathway is most likely through brainstem respiratory motor centres. Air hunger is ameliorated by tidal expansion of the lungs, mainly sensed by pulmonary stretch receptors; thus air hunger may be viewed as a result of the balance between respiratory drive and tidal expansion [24,25]. The chest tightness of asthma seems to arise from receptors in the lungs, stimulated either by chemical mediators or by the change in mechanical environment. This latter form of dyspnoea is thus most closely related to cough in its afferent source. Indeed, there is a variant of asthma whose main symptom is urge to cough; thus, some pulmonary or airway sensory receptors may be common to tightness and cough.

3. Psychophysics

Studies of perception of urge to cough, pain, and dyspnoea share problems of measurement [26]. While mediated by a protective neural system that can be partly assessed through focussed and more generalized methods, all three of these methods are ultimately 'internal feeling' states that are most appropriately assessed by an individual's verbal description of their own experience. The experience is characterized by both sensory qualities and by affective/emotional properties that motivate behaviours to reduce the aversive aspect of the experience. In the case of pain and dyspnoea, the discomfort of many biologists with ''subjective reports'' has fuelled a search for ''objective'' behavioural or physiological measures that avoid perceived problems with self-report. Reflexes, evoked cortical potentials and now functional neuroimaging have been pursued as objective measures of pain and dyspnoea that are 'uncontaminated' by attitudes, biases and the host of other variables that can alter descriptions of experience. However, the objective measure may be a chimera: such physiological outcome measures are currently validated by comparing them to self-report; each measure can be shown to be dissociated from self-report in response to specific interventions. Furthermore, in the end, it is the subjective sensation that the patient cares most about.

To date, research on the mechanisms and treatment of the symptoms of pain, urge to cough and dyspnoea has relied mainly on methods that use 'subjective' report as the dependent variable. These subjective responses are measured using methods of psychophysics, which classically are described as measuring the relationship between sensory perception and the properties of a physical stimulus. Psychophysical measures have long been used to characterize pain and respiratory sensations, but we have found only one published psychophysical study of the urge to cough [27; but see also 28 in this Special Issue]. This study revealed two basic findings: first, there is a graded perceptual intensity of urge to cough that is systematically related to the concentration of irritant substance (capsaicin). Second, urge to cough is perceived at lower stimulus intensity than needed to evoke the cough reflex (although it was not reported whether subjects were attempting to suppress cough, which might have affected this relationship).

Future studies may apply many of the methods used in the measurement of pain and dyspnoea perception to expand these basic findings in cough. Such studies may address the current differences found between sophisticated measures of cough behaviour and subjective measures. Clearly, the same physical event of coughing or dyspnoea can be accompanied by distressing sensation in one situation yet be barely noticeable in another. Future psychophysical studies promise to shed new light on the perceptual dimensions of the urge to cough, the ability to discriminate between stimulus-induced sensations, properties over time such as summation and habituation, sensitivity to treatment interventions and, most importantly, the affective dimension of cough distress and the relevant mechanisms that modulate unpleasantness independently of the intensity of the urge to cough or of the cough itself.

In the case of cough and dyspnoea, we must be careful in thinking about what the source of unpleasantness is—cough may be pleasant if it relieves the urge to cough, which is clearly unpleasant (just as scratching an itch may be pleasant). Likewise, increased breathing may be pleasant if it relieves the unpleasant urge to breath (air hunger).

As biologists, we may also ask what selective advantage perception of these symptoms has: i.e. why is it necessary to build and maintain the cortical structures necessary for perception when reflex mechanisms are available to deal with the biological problem? In the case of cough, we imagine that the perception of urge to cough, which precedes cough itself [27], may allow the animal time to activate inhibitory descending pathways to suppress cough in situations ranging from basic survival to social embarrassment (for instance hiding from a predator or avoiding embarrassment in a concert hall). This perception also allows control over a voluntary cough, which in certain situations may be preferable to a reflexive cough. In the case of dyspnoea, we postulate that perception allows the animal to use complex behaviours when mere motor drive to respiratory muscles is not an appropriate solution to the problem (e.g. the case of urge to breathe in a submerged diving animal). In the case of pain, suppression of normal pain reactions is sometimes required to allow the animal to pursue more important tasks; this has been quantified in animal behaviour experiments [29,30].

4. Summary

The field of pain science is clearly ahead of both dyspnoea and cough sciences. The field of dyspnoea science has shown that it is possible to apply some of the concepts and methods used by pain scientists to a complex respiratory event. It is our hope that the neurophysiological and psychophysical approaches used to understand pain and dyspnoea can be modified to help discoveries about the perception of urge to cough, and the function of afferent and central pathways of cough.

Acknowledgements

Supported in part by DAMD 17-00200018 (Gracely), HL46690 (Banzett) and HL62296 (Undem).

References

[1] Meyer R, et al. Peripheral mechanisms of cutaneous nociception. In: McMahon S, Koltzenburg M, editors. Wall and Melzack's textbook of pain. New York: Elsevier Churchill Livingstone; 2006. p. 3–34.
[2] Canning BJ, Mazzone SB, Meeker SN, Mori N, Reynolds SM, Undem BJ. Identification of the tracheal and laryngeal afferent neurones mediating cough in anaesthetized guinea-pigs. J Physiol 2004;557:543–58.
[3] Addington WR, Stephens RE, Widdicombe JG, Ockey RR, Anderson JW, Miller SP. Electrophysiologic latency to the external obliques of the laryngeal cough expiration reflex in humans. Am J Phys Med Rehab 2003;82:370–3.
[4] Canning BJ, Farmer DG, Mori N. Mechanistic studies of acid-evoked coughing in anesthetized guinea pigs. Am J Physiol Regul Integr Comp Physiol 2006;291:R454–63.
[5] Fuller RW. Pharmacology of inhaled capsaicin in humans. Respir Med 1991;85(Suppl A):31–4.
[6] Carr MJ, Lee L-Y. Plasticity of peripheral mechanisms of cough. Respir Physiol Neurobiol 2006;152:298–311.
[7] Cervero F. Mechanisms of acute visceral pain. Br Med Bull 1991; 47:549–60.
[8] Sarkar S, Hobson AR, Furlong PL, Woolf CJ, Thompson DG, Aziz Q. Central neural mechanisms mediating human visceral hypersensitivity. Am J Physiol Gastrointest Liver Physiol 2001;281:G1196–202.
[9] Campbell JN, Meyer RA. Mechanisms of neuropathic pain. Neuron 2006;52:77–92.
[10] Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. Science 2000;288:1765–9.
[11] Mazzone SB, Canning BJ. Central nervous system control of the airways: pharmacological implications. Curr Opin Pharmacol 2002;2: 220–8.
[12] Mazzone SB, Mori N, Canning BJ. Synergistic interactions between airway afferent nerve subtypes regulating the cough reflex in guinea-pigs. J Physiol 2005;569:559–73.
[13] Ing AJ, Ng MC, Breslin AB. Pathogenesis of chronic persistent cough associated with gastroesophageal reflux. Am J Respir Crit Care Med 1994;149:160–7.
[14] McGarvey LP, Morice AH. Clinical cough and its mechanisms. Respir Physiol Neurobiol 2006;152:363–71.
[15] Tekdemir I, Aslan A, Elhan A. A clinico–anatomic study of the auricular branch of the vagus nerve and Arnold's ear-cough reflex. Surg Radiol Anat 1998;20:253–7.
[16] Whitman BW, Packer RJ. The photic sneeze reflex: literature review and discussion. Neurology 1993;43:868–71.
[17] Banzett R, Moosavi S. Dyspnea and pain: similarities and contrasts between two very unpleasant sensations. Am Pain Soc Bull 2001; 11(1):6–8.
[18] Manning HL, Schwartzstein RM. Pathophysiology of dyspnea. [Review]. N Engl J Med 1995;333:1547–53.
[19] Moy ML, Woodrow Weiss J, Sparrow D, Israel E, Schwartzstein RM. Quality of dyspnea in bronchoconstriction differs from external resistive loads. Am J Respir Crit Care Med 2000;162:451–5.
[20] Lansing RW, Im BS, Thwing JI, Legedza AT, Banzett RB. The perception of respiratory work and effort can be independent of the perception of air hunger. Am J Respir Crit Care Med 2000;162: 1690–6.
[21] Killian KJ, Gandevia SC, Summers E, Campbell EJM. Effect of increased lung volume on perception of breathlessness, effort, and tension. J Appl Physiol: Respir Environ Exerc Physiol 1984;57: 686–91.

[22] Stubbing DG, Ramsdale EH, Killian KJ, Campbell EJM. Psychophysics of inspiratory muscle force. J Appl Physiol: Respir Environ Exerc Physiol 1983;54:1216–21.
[23] Banzett RB, Lansing RW, Brown R, Topulus GP, Yager D, Steele SM, et al. 'Air hunger' from increased PCO_2 persists after complete neuromuscular block in humans. Respir Physiol 1990;81:1–17.
[24] Manning HL, et al. Reduced tidal volume increases 'air hunger' at fixed PCO_2 in ventilated quadriplegics. Respir Physiol 1992;90:19–30.
[25] Hill L, Flack F. The effect of excess of carbon dioxide and of want of oxygen upon the respiration and the circulation. J. Physiol 1908;37:77–111.
[26] Lansing R, Banzett R. Psychophysical methods in the study of respiratory sensation. In: Adams L, Guz A, editors. Respiratory sensation. New York: Marcel Dekker; 1996. p. 69–100.
[27] Davenport PW, Sapienza CM, Bolser DC. Psychophysical assessment of the urge-to-cough. Eur Respir Rev 2002;12:249–53.
[28] Davenport PW, Bolser DC, Vickroy T, Berry R, Martin AD, Hey JA, et al. The effect of codeine on the urge-to-cough response to inhaled capsaicin. Pulm Pharmacol Ther 2007; this issue, doi:10.1016/j.pupt.2006.10.012.
[29] Amit Z, Galina ZH. Stress-induced analgesia: adaptive pain suppression. Physiol Rev 1986;66:1091–120.
[30] Foo H, Mason P. Sensory suppression during feeding. Proc Natl Acad Sci USA 2005;102:16865–9.

Neurobiology of Disease

Decreased Central μ-Opioid Receptor Availability in Fibromyalgia

Richard E. Harris,[1] Daniel J. Clauw,[1] David J. Scott,[2] Samuel A. McLean,[3] Richard H. Gracely,[1] and Jon-Kar Zubieta[2,4]

[1]Department of Internal Medicine, [2]Department of Psychiatry and Molecular and Behavioral Neuroscience Institute, and Departments of [3]Emergency Medicine and [4]Radiology, The University of Michigan, Ann Arbor, Michigan 48109

The underlying neurophysiology of acute pain is fairly well characterized, whereas the central mechanisms operative in chronic pain states are less well understood. Fibromyalgia (FM), a common chronic pain condition characterized by widespread pain, is thought to originate largely from altered central neurotransmission. We compare a sample of 17 FM patients and 17 age- and sex-matched healthy controls, using μ-opioid receptor (MOR) positron emission tomography. We demonstrate that FM patients display reduced MOR binding potential (BP) within several regions known to play a role in pain modulation, including the nucleus accumbens, the amygdala, and the dorsal cingulate. MOR BP in the accumbens of FM patients was negatively correlated with affective pain ratings. Moreover, MOR BP throughout the cingulate and the striatum was also negatively correlated with the relative amount of affective pain (McGill, affective score/sensory score) within these patients. These findings indicate altered endogenous opioid analgesic activity in FM and suggest a possible reason for why exogenous opiates appear to have reduced efficacy in this population.

Key words: **fibromyalgia; opioid; pain; chronic; positron emission tomography; μ**

Introduction

Sensory perceptions can serve to alert organisms of present and/or future danger. This is particularly evident for the sensation of acute pain. However, neural pain pathways that originally function to warn of potential harm may also become dysfunctional and lead to maladaptive diseased states of a chronic nature (Woolf, 2004). Fibromyalgia (FM), a condition of idiopathic chronic pain, may be one such disorder.

FM is defined on the basis of tenderness and spontaneous chronic widespread pain (Wolfe et al., 1990) and afflicts 2–4% of individuals in industrialized countries (Wolfe et al., 1995). In addition many FM patients also suffer from psychiatric illnesses such as depression (Giesecke et al., 2003). Unfortunately, because of the lack of readily identifiable peripheral pathology in FM (e.g., muscle or joint inflammation), acceptance of this condition by medical practitioners has been slow (Cohen, 1999).

A growing body of scientific literature suggests that the lack of apparent peripheral pathology in FM might be explained by a primary disturbance in central rather than peripheral pain processing (Clauw and Chrousos, 1997). Data from psychophysical pain testing (Petzke et al., 2003), quantitative EEG (Lorenz et al., 1996), and functional neuroimaging (Gracely et al., 2002; Cook et al., 2004) supports this theory. FM patients display increased neural activations in pain regions such as the insula, the somatosensory cortex, and the cingulate, in response to pressure pain. These same areas are activated in healthy control participants, albeit at higher objective stimulus intensities. Although this suggests that altered pain processing of experimental stimuli occurs in FM, the underlying neurobiology driving clinical symptoms such as pain and depression is unknown.

One potential reason for pain symptoms in FM may be inadequate descending antinociceptive activity. Research suggests that such activity may be deficient or absent in FM (Julien et al., 2005). In humans, the two principal descending inhibitory pain pathways involve either norepinephrine/serotonin or opioids, but psychophysical studies are incapable of distinguishing which of these pathways may be affected. FM patients display low CSF levels of biogenic amines, suggesting a possible deficiency of descending serotonergic/noradrenergic pathways in this condition (Russell et al., 1992). CSF levels of endogenous enkephalins, however, have been noted to be high, which suggests an excess of endogenous opioids in FM (Baraniuk et al., 2004). Although no trials of exogenous opioids in FM have been performed, opioids are not anecdotally found to be useful in treating this and related conditions (Rao and Clauw, 2004). Thus, existing data support a deficit in descending analgesic activity in the serotonergic/noradrenergic system and an overactive opioidergic system; however, as of yet, there is no direct evidence of this.

We used positron emission tomography (PET) to further investigate opioid antinociceptive activity in FM. [^{11}C]carfentanil, a selective μ-opioid receptor (MOR) radiotracer, was used to

Received May 7, 2007; revised Aug. 1, 2007; accepted Aug. 2, 2007.

This work was supported by Department of Army Grant DAMD-17/002-0018, Grant M01-RR000042 from the National Center for Research Resources, a component of the National Institutes of Health (NIH), and NIH Grant R01 AT 001415 (J.-K.Z.). R.E.H. was supported by NIH–National Center for Complementary and Alternative Medicine Grant K01 AT01111-01. S.A.M. was supported by NIH Grant K12 RR017607-01. There are no conflicts of interest for any of us with the material presented. We acknowledge V. Napadow and S. Harte for their careful review of this manuscript.

Correspondence should be addressed to Dr. Richard E. Harris, Chronic Pain and Fatigue Research Center, 24 Frank Lloyd Wright Drive, P.O. Box 385, Lobby M, Ann Arbor, MI 48106. E-mail: reharris@med.umich.edu.

DOI:10.1523/JNEUROSCI.2849-07.2007

 0270-6474/07/2710000-07$15.00/0

assess baseline receptor availability *in vivo* [binding potential (BP)] in patients and pain-free control participants. We hypothesized that patients with FM may have decreased MOR receptor availability, because they have increased levels of endogenous opioids in the CSF (Baraniuk et al., 2004), possibly leading to receptor downregulation. In addition, we investigated the association of MOR availability with both the affective and sensory dimensions of clinical pain. Finally, as an exploratory analysis, we examined the relationship between MOR availability and depression within FM patients.

Materials and Methods

Participants

As part of an ongoing study investigating the impact of acupuncture treatment in FM, 17 female right-handed patients (age, 44.8 ± 13.7 years; duration of FM diagnosis, 8.4 ± 6.0 years) were examined with PET. Seventeen right-handed age- and sex-matched control participants (age, 40.4 ± 11.2 years) were used as a comparison with the FM group. All analyses were performed on data acquired before acupuncture treatment. Participants gave written informed consent, and the study protocol was approved by the local Institutional Review Board and the Radioactive Drug Research Committee.

All patients (1) met the American College of Rheumatology 1990 criteria (Wolfe et al., 1990) for the diagnosis of FM for at least 1 year; (2) had continued presence of pain >50% of days; (3) were willing to limit the introduction of any new medications or treatment modalities for control of FM symptoms during the study; (4) were >18 and <75 years of age; (5) were female; (6) were right handed; (7) had no alcohol intake 48 h before PET studies; and (8) were capable of giving written informed consent. Patients were excluded if they (1) had used narcotic analgesics within the past year or had a history of substance abuse; (2) had presence of a known coagulation abnormality, thrombocytopenia, or bleeding diathesis; (3) had the presence of concurrent autoimmune or inflammatory disease, such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, etc., that causes pain; (4) had concurrent participation in other therapeutic trials; (5) were pregnant or nursing mothers; (6) had severe psychiatric illnesses (current schizophrenia, major depression with suicidal ideation, or substance abuse within 2 years); (7) had current major depression; or (8) had contraindications to PET. No patients were taking or had a previous history of opioid medication use. Ten of the FM participants were taking either serotonin reuptake inhibitors or dual serotonin/norepinephrine reuptake inhibitors, whereas seven were not.

All healthy controls were (1) female; (2) right handed; (3) between the ages of 18 and 60; and (4) had no chronic medical illnesses.

Neuroimaging

Image acquisition. PET scans were acquired with a Siemens (Knoxville, TN) HR^+ scanner in three-dimensional mode [reconstructed full-width at half-maximum (FWHM) resolution, ~5.5 mm in-plane and 5.0 mm axially], with septa retracted and scatter correction. Participants were positioned in the PET scanner gantry, and an intravenous (antecubital) line was placed in the right arm. A light forehead restraint was used to eliminate intrascan head movement. [^{11}C]carfentanil was synthesized at high specific activity (>2000 Ci/mmol) by the reaction of [^{11}C]methyliodide and a nonmethyl precursor as described previously (Dannals et al., 1985), with minor modifications to improve its synthetic yield (Jewett, 2001); 10–15 mCi (370–555 MBq) were administered during the scan. Receptor occupancy by carfentanil was calculated to be between 0.2 and 0.6% for brain regions with low, intermediate, and high MOR concentrations, based on the mass of carfentanil administered and the known concentration of opioid receptors in the postmortem human brain (Gross-Isseroff et al., 1990; Gabilondo et al., 1995). Fifty percent of the [^{11}C]carfentanil dose was administered as a bolus, and the remaining 50% was administered by continuous infusion for the remainder of the study. Twenty-eight frames of images were acquired over 90 min with an increasing duration (30 s up to 10 min).

Anatomical magnetic resonance imaging (MRI) scans were acquired in all subjects on a 3 tesla scanner (Signa LX; General Electric, Milwaukee, WI). Acquisition sequences were axial SPGR IR-Prep magnetic resonance (MR) (echo time, 3.4 ms; repetition time, 10.5 ms; inversion time, 200 ms; flip angle, 20°; number of excitations, 1; number of contiguous images, 124; thickness, 1.5 mm).

Image processing. PET images were reconstructed using iterative algorithms (brain mode; FORE/OSEM, four iterations, 16 subsets; no smoothing) into a 128 × 128 pixel matrix in a 28.8 cm diameter field of view. Attenuation correction was performed through a 6 min transmission scan (^{68}Ge source) obtained before the PET study and with iterative reconstruction of the blank/transmission data followed by segmentation of the attenuation image. Small head motions during emission scans were corrected by an automated computer algorithm for each subject before analysis, and the images were coregistered to each other with the same software (Minoshima et al., 1993). Time points were then decay corrected during reconstruction of the PET data. Image data were transformed on a voxel-by-voxel basis into two sets of parametric maps: (1) a tracer transport measure (K_1 ratio) and (2) a receptor-related measure at equilibrium [distribution volume ratio (DVR)]. To avoid the need for arterial blood sampling, the tracer transport and binding measures were calculated using a modified Logan graphical analysis (Logan et al., 1996), using the occipital cortex (an area devoid of MORs) as the reference region. The slope of the Logan plot was used for the estimation of the DVR, a measure equal to the $(f_2B_{max}/K_d) + 1$ for this receptor site and radiotracer. f_2B_{max}/K_d (or DVR − 1) is the receptor-related measure (BP or MOR availability). The term f_2 refers to the concentration of free radiotracer in the extracellular fluid and is considered to represent a constant and very small value. K_1 and DVR images for each experimental period and MR images were coregistered to each other and to the International Consortium for Brain Mapping (ICBM) stereotactic atlas orientation. The accuracy of coregistration and nonlinear warping algorithms was confirmed for each subject individually by comparing the transformed MRI and PET images to each other and the ICBM atlas template.

Group differences were mapped into stereotactic space using *t* maps of statistical significance with SPM2 (Wellcome Department of Cognitive Neurology, London, UK) and Matlab (MathWorks, Natick, MA) software, with a general linear model. No global normalization was applied to the data, and therefore the calculations presented are based on absolute f_2B_{max}/K_d estimates. Only regions with specific MOR BP were included in the analyses (i.e., voxels with DVR values >1.1). To compensate for small residual anatomic variations across subjects and to improve signal-to-noise ratios, a three-dimensional Gaussian filter (FWHM, 6 mm) was applied to each scan.

Image analysis. The comparisons between patients and control subjects were performed using two-sample *t* tests, on a voxel-by-voxel basis within SPM2. Significant effects were detected using a statistical threshold that controls a type I error rate at $p = 0.05$, corrected for multiple comparisons. These statistical thresholds were estimated using the Euler characteristic (Worsley et al., 1992) based on the number of voxels in the gray matter and image smoothness and the extent of local changes (correction for cluster volume) (Friston et al., 1991). Correlations between MOR BP and the relative amount of the affective quality of clinical pain were made using a regression model on a voxel-by-voxel basis with SPM2. Significant effects were detected using a cluster-corrected threshold *p* value of 0.05.

Numerical values for MOR binding were extracted from the image data by averaging the values of voxels contained in the area in which significant effects were obtained in the analyses. These values were then entered into SPSS version 14.0 (SPSS, Chicago, IL) for plotting, to rule out the presence of outliers, and to perform correlations with clinical measures.

Global BP values were also extracted and compared between groups with Student's *t* test. Because global values were found to be lower in the patients (see Results), global values were used as a covariate in regression analyses in which MOR BP was used as the dependent variable and group status and global BP were independent variables. This allows an estimate of group differences for a specific region, while controlling for differences

in global scores. To examine effects of concomitant drug usage in the patients, additional regression analyses were performed in which MOR BP was again used as the dependent variable and clinical pain and drug usage (either taking or not taking reuptake inhibitors; see above) were added as covariates. This final procedure was used to examine the effect of drug usage in the patient group on the relationship between MOR BP and pain.

Clinical assessment

Clinical pain. Clinical pain was assessed immediately before the PET scan with the Short Form of the McGill Pain Questionnaire (SF MPQ) (Melzack, 1987). The SF MPQ has two subscales that measure "sensory" and "affective" qualities of pain. To assess the relative contribution of the affective dimension of pain, the affective subscore of the SF MPQ was divided by the sensory subscore (affective/sensory). This yields an estimate of the relative contribution of the affective component of pain while controlling for the sensory intensity of the sensation (Petzke et al., 2005). For comparison, we also calculated the ratio of the sensory versus the affective subscores of the SF MPQ (i.e., sensory/affective).

Psychological assessment. Depressive symptoms were assessed with the Center for Epidemiological Studies-Depression Scale (Radloff, 1977). This is a 20-item self-report instrument that was developed by the National Institute of Mental Health to detect major or clinical depression in adolescents and adults in both clinical and normal populations. The total score was used for correlation with MOR BP.

Results

As expected, no significant differences were observed between the FM group and the control group with respect to participant age or sex (all $p > 0.05$). During PET imaging, FM patients exhibited significant reductions in MOR BP compared with controls in four regions: the bilateral nucleus accumbens (NAc; left, $p < 0.02$; right, $p < 0.05$; corrected for multiple comparisons), the left amygdala ($p < 0.05$; corrected for multiple comparisons), and the right dorsal anterior cingulate ($p < 0.05$; corrected for multiple comparisons) (Fig. 1*A–C*; Table 1). Global mean MOR BP values were reduced in the patient group ($p < 0.01$). Because a reduction in global BP value could explain the lower BP values within these regions for the FM participants, we performed regression analyses using regional MOR BP values as the dependent variable and group assignment and global BP as covariates. Both the left ($p < 0.001$) and right ($p < 0.05$) nucleus accumbens and the amygdala ($p < 0.005$) showed reduced MOR BP in the patients after controlling for global BP differences. The dorsal anterior cingulate showed a trend toward significance ($p < 0.07$). These data suggest that FM patients have reduced MOR BP within multiple brain regions.

To assess whether drug usage within the FM participants could be responsible for reduced MOR BP values, we examined the mean MOR BP for each of the above regions in FM participants that were either taking or not taking serotonin reuptake inhibitors or dual serotonin/norepinephrine reuptake inhibitors. No differences in BP were detected for any of these regions between patients that were either taking or not taking this class of drugs (all $p > 0.35$). These analyses suggest that the reduced binding observed in the patients for these regions is not attributable to medication usage.

Within the FM patients, MOR BP binding in the left NAc was negatively correlated with clinical pain ratings in the affective (Fig. 2) (SF MPQ affective score, $r = -0.53$; $p < 0.05$) but not the sensory (SF MPQ sensory score, $r = -0.13$; $p > 0.50$) dimension of pain. Drug usage, when added as a covariate, did not significantly alter this relationship (standardized β without drug covariate $= -0.44$; with drug covariate, $\beta = -0.45$; significance of difference, $p = 0.59$). No statistically significant correlations were observed between clinical pain ratings and the right accumbens, the left amygdala, or the right dorsal anterior cingulate BP of FM patients (all $p > 0.05$). A significant negative correlation between MOR BP and depressive symptoms was also observed within the amygdala (Table 2).

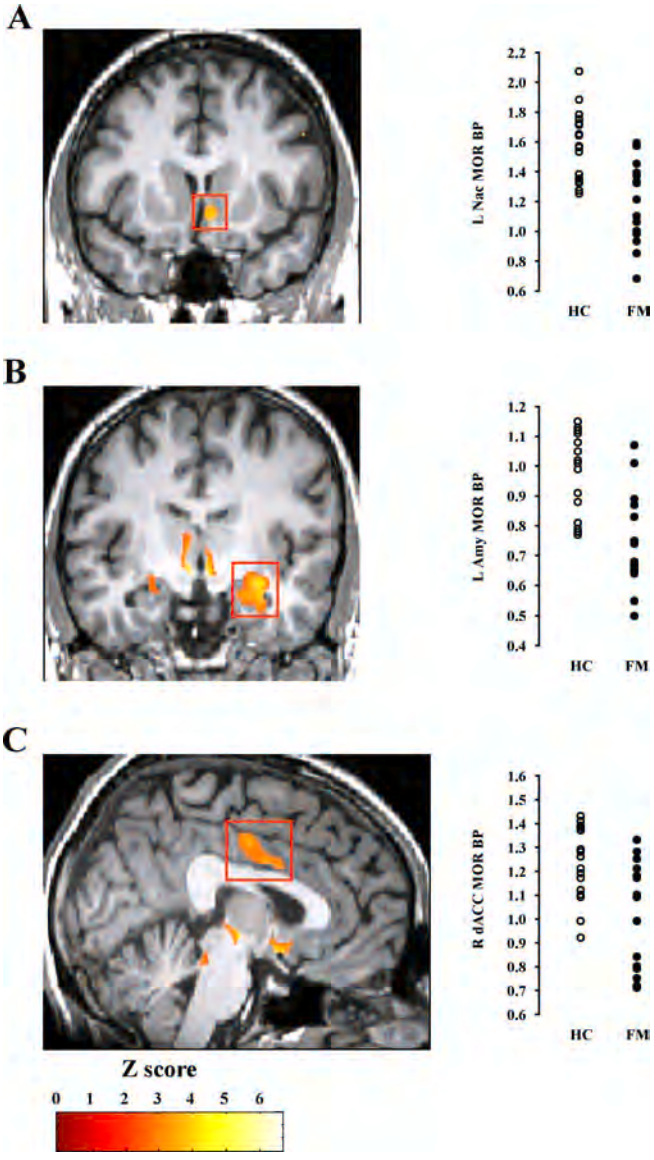


Figure 1. Reduced MOR BP in FM patients. ***A–C***, Regions showing reduced MOR BP: left NAc (L Nac; ***A***), left amygdala (L Amy; ***B***), and right dACC (R dACC; ***C***). Plots of individual MOR BP values extracted from PET images are depicted to the right of each corresponding region of interest. FM and healthy control (HC) participants are shown in black and white circles, respectively.

Because MOR BP within the accumbens was associated with the affective dimension of pain, more so than the sensory dimension, we next investigated the relationship between MOR BP and the relative amount of affective versus sensory pain (SF MPQ, affective score/sensory score). Interindividual differences in MOR binding throughout the cingulate [dorsal anterior (dACC), $p < 0.05$; posterior (pCC), $p < 0.001$; and, to a lesser extent, anterior (aCC), $p = 0.09$; all corrected for multiple comparisons] were negatively correlated with the relative amount of affective pain (Fig. 3*A*,*B*, Table 3). Similar findings were detected within the right ventral putamen (Fig.

Table 1. Regions of reduced [^{11}C]carfentanil binding in FM patients

Brain region	MNI coordinates (*x*, *y*, *z*)	*Z*	Cluster size (mm^3)	%Δ Binding potential (HC − FM; mean ± SD)
NAc (l)	9, 7, −11	4.1*	159	24.7 ± 15.3
NAc (r)	−18, 6, −12	3.3*	140	18.1 ± 13.3
Amygdala (l)	29, −10, −13	3.7*	269	23.7 ± 14.6
dACC (r)	−4, −11, 43	3.1*	182	17.7 ± 12.5

*$p < 0.05$, corrected. MNI, Montreal Neurological Institute; l, left; r, right.

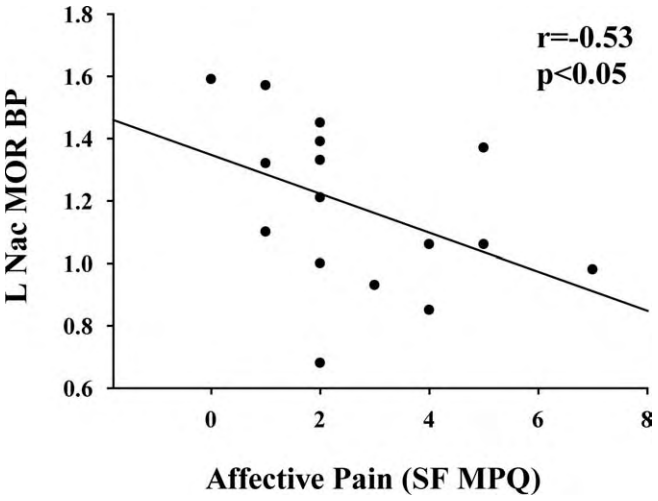


Figure 2. MOR BP is negatively correlated with affective pain. The scatter plot of left accumbens (L Nac) MOR BP and clinical pain (SF MPQ, affective score) reveals a significant negative correlation ($r = -0.53$; $p < 0.05$).

Table 2. Correlations between MOR availability and depression ratings in FM

Brain region	*Rho* value
NAc (l)	−0.25
NAc (r)	0.16
Amygdala (l)	−0.49*
dACC (r)	−0.21

*$p < 0.05$. l, Left; r, right.

3*C*). The primary somatosensory cortex and the insula also showed a negative correlation with MOR BP; however, these regions did not reach significance after correction for multiple comparisons ($p > 0.05$). Adding medication usage as a covariate did not significantly alter the relationship between affective/sensory scores and MOR BP for any of these regions (all percentage differences in standardized βs with and without covariate $\leq$ 1.3%; all significance of change, $p > 0.20$). No significant negative correlations were observed between MOR BP and the relative amount of sensory pain (SF MPQ, sensory score/affective score) within any brain regions (all $p > 0.05$). No correlations were observed between MOR BP within any of these regions and depressive symptoms (all $p > 0.20$). These results suggest that in FM patients the affective quality of pain is associated with reduced MOR availability throughout the cingulate and other brain regions commonly associated with pain modulation.

Discussion

Our data indicate that FM patients have reduced MOR BP within structures typically observed in imaging studies of experimental pain involving healthy control participants. These structures include the amygdala, the cingulate, and the nucleus accumbens.

All of these regions have previously been noted to play some role in nociception and pain. Opioid activity in the nucleus accumbens and the amygdala has been shown to modulate nociceptive neural transmission in animal models of pain (Gear and Levine, 1995; Manning, 1998). Indeed, endogenous opioids play a central role in analgesia and the perception of painful stimuli (Fields, 2004). MOR-mediated neurotransmission in the nucleus accumbens and amygdala has also been shown to be modulated by pain in healthy controls reducing the pain experience (Zubieta et al., 2001), in a manner consistent with animal data. Because the concentration of endogenous opioids is elevated in the CSF of FM patients (Baraniuk et al., 2004), MORs may be highly occupied by endogenous ligand in an attempt to reduce pain or downregulated after prolonged stimulation. Both these effects could explain the reduced MOR BP observed in this study.

An investigation using functional magnetic resonance imaging (fMRI) in FM has associated enhanced neural activity in both the amygdala and the cingulate with depressive symptoms (Giesecke et al., 2005). This further supports the notion that these regions may be involved with evaluating affective aspects of pain and is consistent with our findings of reduced MOR BP within the amygdala and its correlation with depressive symptoms. Indeed, the dorsal anterior cingulate region, identified as having reduced MOR BP in the patients, also showed a negative correlation with the affective dimension of pain (albeit in the opposite hemisphere). These data suggest that MOR availability within the dorsal anterior cingulate is related to the affective dimension of pain. This finding is supported by previous imaging studies of the cingulate (Vogt, 2005).

Two other chronic pain states, rheumatoid arthritis (Jones et al., 1994) and central neuropathic pain following stroke (Jones et al., 2004; Willoch et al., 2004), also display a reduction in opioid receptor BP within the CNS, as measured with the nonselective opioid receptor radiotracer [^{11}C]diprenorphine. Although these data may then suggest that reduced opioid receptor availability may be a shared feature across chronic pain states, the regional distribution of reduced receptor binding was dissimilar across these studies and pain conditions. In rheumatoid arthritis pain, reduced opioid receptor binding was observed in the cingulate, frontal, and temporal cortices, whereas for central neuropathic pain, reduced opioid receptor availability was detected primarily within the thalamus, somatosensory cortex, cingulate, and insula. In patients with peripheral neuropathic pain, reduced opioid BP has been observed bilaterally across brain hemispheres, whereas in central neuropathic pain, reductions in BP were observed largely isolated to one hemisphere (Maarrawi et al., 2007). This heterogeneous pattern of reduced binding may reflect different underlying mechanisms operating in these diverse pain conditions. In the case of FM the reductions in MOR BP observed were localized in regions known to be involved in antinociception in animal models (Gear and Levine, 1995; Manning,

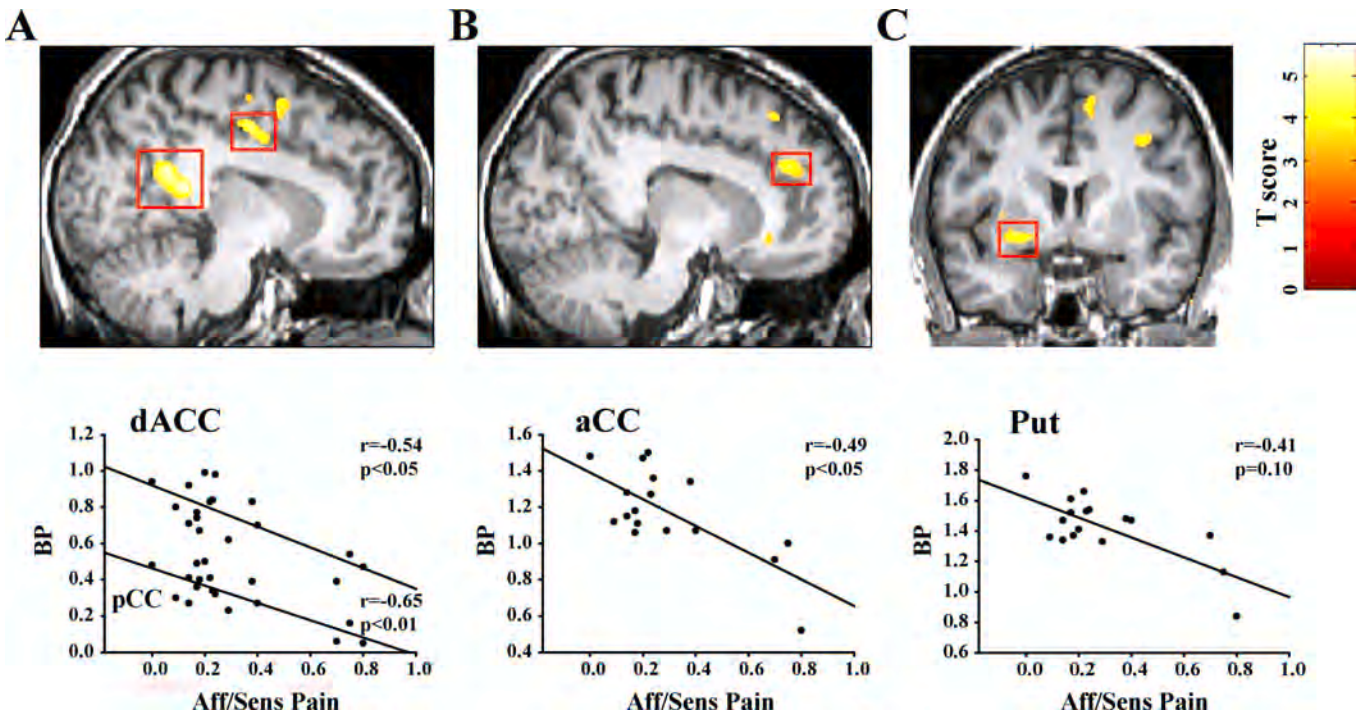


Figure 3. Relative magnitude of the affective pain dimension is associated with reduced MOR BP throughout the cingulate and striatum in FM. ***A–C***, Regions showing significant correlations with SF MPQ affective/sensory (Aff/Sens) scores: left dACC and pCC (***A***), right aCC (***B***), and right putamen (Put; ***C***). Scatter plots of individual MOR BP values extracted from PET images are plotted against affective/sensory scores below each image.

Table 3. Regions of correlated MOR BP and relative amount of affective versus sensory pain

Brain region	MNI coordinates (*x*, *y*, *z*)	*Z*	Cluster size (mm^3)	*Rho* value for extracted ROIs
dACC (l)	10, −11, 48	3.75**	1001	−0.54
pCC (l)	10, −44, 17	4.11***	936	−0.65
aCC (r)	−12, 38, 28	3.44*	410	−0.49
Putamen (r)	−26, 4, −8	3.36**	517	−0.41

*$p = 0.09$, corrected; **$p < 0.05$, corrected; ***$p < 0.001$, corrected. MNI, Montreal Neurological Institute; ROIs, regions of interest.

1998), as well as pain and emotion regulation, including the affective quality of pain, in humans (Rainville et al., 1997; Zubieta et al., 2001, 2003) (i.e., dorsal anterior cingulate, nucleus accumbens, and amygdala).

Prolonged activations of the MOR by sustained elevations of endogenous agonist have been shown to result in a subsequent decrease in the concentration of MORs in animal models of chronic pain (Li et al., 2005). Chronic administration of morphine may reduce MOR functioning possibly by altering the ability of the receptor to bind to G-proteins, whereas other agonists also downregulate and internalize these receptors (Whistler et al., 1999). If this were the case in FM, sustained activation of MORs by endogenous agonists could ultimately lead to a downregulation of MOR receptor concentration, function, or both. Therefore both mechanisms (i.e., increased release of endogenous opioids and/or a reduction in receptor function) could be responsible for our findings.

We also observed a negative correlation between MOR BP within the accumbens and clinical ratings in the affective dimension of pain. This supports the hypothesis that mechanisms of clinical FM pain are coupled to MOR availability. A strong relationship between pain affect and MOR BP was also observed throughout multiple regions of the cingulate. This is consistent with a proposed role of the dorsal and anterior cingulate in the modulation of pain perception via opioidergic mechanisms (Vogt et al., 1995). Recent investigations of opioid receptor binding in healthy controls showed reduced receptor availability within the rostral cingulate during thermal pain (Sprenger et al., 2006) and sustained muscular pain, which correlated with the suppression of pain affect (Zubieta et al., 2001). Within animal models of experimental pain, microinjection of morphine into the anterior cingulate dose-dependently reduced affective components of pain greater than sensory aspects (LaGraize et al., 2006). Our findings of greater affective pain associated with lower MOR BP within the cingulate are consistent with these observations.

We also detected a negative correlation between affective pain and MOR BP values within the posterior cingulate. This is potentially a novel finding because this region is not typically observed in pain imaging trials in humans (Vogt, 2005). However previous trials do suggest that activity within the posterior cingulate, specifically the dorsal aspect, is related to skeletomotor orientation of the body in response to noxious stimuli (Vogt, 2005; Vogt and Laureys, 2005). Because our FM participants experienced clinical pain during the scanning sessions, one could speculate that reduced MOR BP within this region may reflect activation of the endogenous opioid system in an attempt to reduce skeletomotor orientation resulting from spontaneous clinical pain. One additional potential lim-

itation of this final analysis is that affective and sensory pain dimensions are often highly correlated.

A significant relationship was also detected between MOR availability within the amygdala and depression. Individuals with more depressive symptoms had reductions in MOR BP within the amygdala. This finding is not unexpected, because reduced opioid receptor availability within the amygdala has been previously associated with periods of sadness in patients with major depressive disorder (Kennedy et al., 2006).

Perhaps more important for clinical investigations in FM, our results would predict a lack of efficacy for exogenous opioids in this population. Regardless of whether endogenous opioids are high (Baraniuk et al., 2004) or MORs are downregulated, both scenarios would predict that FM patients would respond less well to exogenous opioids. This prediction awaits future prospective trials of exogenous opioid treatments in FM.

Overall we detect decreased MOR availability in FM patients, demonstrating a dysregulation of this neurotransmitter system in this disease. The reduction in binding was further negatively correlated with affective pain. The observation of specific regional alterations in central opioid neurotransmission in FM suggests that these mechanisms, possibly as a consequence of persistent pain, are involved in the clinical presentation and even the perpetuation of symptoms in this illness. Furthermore, because these receptors are the target of opiate drugs, a profound reduction in the concentration or function of these receptors is consistent with a poor response of FM patients to this class of analgesics, observed anecdotally in clinical settings.

References

Baraniuk JN, Whalen G, Cunningham J, Clauw DJ (2004) Cerebrospinal fluid levels of opioid peptides in fibromyalgia and chronic low back pain. BMC Musculoskelet Disord 5:48.

Clauw DJ, Chrousos GP (1997) Chronic pain and fatigue syndromes: overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. Neuroimmunomodulation 4:134–153.

Cohen ML (1999) Is fibromyalgia a distinct clinical entity? The disapproving rheumatologist's evidence. Baillieres Best Pract Res Clin Rheumatol 13:421–425.

Cook DB, Lange G, Ciccone DS, Liu WC, Steffener J, Natelson BH (2004) Functional imaging of pain in patients with primary fibromyalgia. J Rheumatol 31:364–378.

Dannals RF, Ravert HT, Frost JJ, Wilson AA, Burns HD, Wagner Jr HN (1985) Radiosynthesis of an opiate receptor binding radiotracer: [11C]carfentanil. Int J Appl Radiat Isot 36:303–306.

Fields H (2004) State-dependent opioid control of pain. Nat Rev Neurosci 5:565–575.

Friston KJ, Frith CD, Liddle PF, Frackowiak RS (1991) Comparing functional (PET) images: the assessment of significant change. J Cereb Blood Flow Metab 11:690–699.

Gabilondo AM, Meana JJ, Garcia-Sevilla JA (1995) Increased density of mu-opioid receptors in the postmortem brain of suicide victims. Brain Res 682:245–250.

Gear RW, Levine JD (1995) Antinociception produced by an ascending spino-supraspinal pathway. J Neurosci 15:3154–3161.

Giesecke T, Williams DA, Harris RE, Cupps TR, Tian X, Tian TX, Gracely RH, Clauw DJ (2003) Subgrouping of fibromyalgia patients on the basis of pressure-pain thresholds and psychological factors. Arthritis Rheum 48:2916–2922.

Giesecke T, Gracely RH, Williams DA, Geisser M, Petzke F, Clauw DJ (2005) The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort. Arthritis Rheum 52:1577–1584.

Gracely RH, Petzke F, Wolf JM, Clauw DJ (2002) Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 46:1333–1343.

Gross-Isseroff R, Dillon KA, Israeli M, Biegon A (1990) Regionally selective increases in mu opioid receptor density in the brains of suicide victims. Brain Res 530:312–316.

Jewett DM (2001) A simple synthesis of [11C]carfentanil using an extraction disk instead of HPLC. Nucl Med Biol 28:733–734.

Jones AK, Cunningham VJ, Ha-Kawa S, Fujiwara T, Luthra SK, Silva S, Derbyshire S, Jones T (1994) Changes in central opioid receptor binding in relation to inflammation and pain in patients with rheumatoid arthritis. Br J Rheumatol 33:909–916.

Jones AK, Watabe H, Cunningham VJ, Jones T (2004) Cerebral decreases in opioid receptor binding in patients with central neuropathic pain measured by [11C]diprenorphine binding and PET. Eur J Pain 8:479–485.

Julien N, Goffaux P, Arsenault P, Marchand S (2005) Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain 114:295–302.

Kennedy SE, Koeppe RA, Young EA, Zubieta JK (2006) Dysregulation of endogenous opioid emotion regulation circuitry in major depression in women. Arch Gen Psychiatry 63:1199–1208.

LaGraize SC, Borzan J, Peng YB, Fuchs PN (2006) Selective regulation of pain affect following activation of the opioid anterior cingulate cortex system. Exp Neurol 197:22–30.

Li Z, Proud D, Zhang C, Wiehler S, McDougall JJ (2005) Chronic arthritis down-regulates peripheral mu-opioid receptor expression with concomitant loss of endomorphin 1 antinociception. Arthritis Rheum 52:3210–3219.

Logan J, Fowler JS, Volkow ND, Wang GJ, Ding YS, Alexoff DL (1996) Distribution volume ratios without blood sampling from graphical analysis of PET data. J Cereb Blood Flow Metab 16:834–840.

Lorenz J, Grasedyck K, Bromm B (1996) Middle and long latency somatosensory evoked potentials after painful laser stimulation in patients with fibromyalgia syndrome. Electroencephalogr Clin Neurophysiol 100:165–168.

Maarrawi J, Peyron R, Mertens P, Costes N, Magnin M, Sindou M, Laurent B, Garcia-Larrea L (2007) Differential brain opioid receptor availability in central and peripheral neuropathic pain. Pain 127:183–194.

Manning BH (1998) A lateralized deficit in morphine antinociception after unilateral inactivation of the central amygdala. J Neurosci 18:9453–9470.

Melzack R (1987) The short-form McGill Pain Questionnaire. Pain 30:191–197.

Minoshima S, Koeppe RA, Mintun MA, Berger KL, Taylor SF, Frey KA, Kuhl DE (1993) Automated detection of the intercommissural line for stereotactic localization of functional brain images. J Nucl Med 34:322–329.

Petzke F, Clauw DJ, Ambrose K, Khine A, Gracely RH (2003) Increased pain sensitivity in fibromyalgia: effects of stimulus type and mode of presentation. Pain 105:403–413.

Petzke F, Harris RE, Williams DA, Clauw DJ, Gracely RH (2005) Differences in unpleasantness induced by experimental pressure between patients with fibromyalgia and controls. Eur J Pain 9:325–335.

Radloff LS (1977) The CES-D Scale: a self-report depression scale for research in the general population. Applied Psychological Measurement 1:385–401.

Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC (1997) Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science 277:968–971.

Rao SG, Clauw DJ (2004) The management of fibromyalgia. Drugs Today (Barc) 40:539–554.

Russell IJ, Vaeroy H, Javors M, Nyberg F (1992) Cerebrospinal fluid biogenic amine metabolites in fibromyalgia/fibrositis syndrome and rheumatoid arthritis. Arthritis Rheum 35:550–556.

Sprenger T, Valet M, Boecker H, Henriksen G, Spilker ME, Willoch F, Wagner KJ, Wester HJ, Tolle TR (2006) Opioidergic activation in the medial pain system after heat pain. Pain 122:63–67.

Vogt BA (2005) Pain and emotion interactions in subregions of the cingulate gyrus. Nat Rev Neurosci 6:533–544.

Vogt BA, Laureys S (2005) Posterior cingulate, precuneal and retrosplenial cortices: cytology and components of the neural network correlates of consciousness. Prog Brain Res 150:205–217.

Vogt BA, Wiley RG, Jensen EL (1995) Localization of mu and delta opioid receptors to anterior cingulate afferents and projection neurons and input/output model of mu regulation. Exp Neurol 135:83–92.

Whistler JL, Chuang HH, Chu P, Jan LY, von Zastrow M (1999) Functional dissociation of mu opioid receptor signaling and endocytosis: implica-

tions for the biology of opiate tolerance and addiction. Neuron 23:737–746.

Willoch F, Schindler F, Wester HJ, Empl M, Straube A, Schwaiger M, Conrad B, Tolle TR (2004) Central poststroke pain and reduced opioid receptor binding within pain processing circuitries: a [11C]diprenorphine PET study. Pain 108:213–220.

Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P (1990) The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 33:160–172.

Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L (1995) The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 38:19–28.

Woolf CJ (2004) Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med 140:441–451.

Worsley KJ, Evans AC, Marrett S, Neelin P (1992) A three-dimensional statistical analysis for CBF activation studies in human brain. J Cereb Blood Flow Metab 12:900–918.

Zubieta JK, Smith YR, Bueller JA, Xu Y, Kilbourn MR, Jewett DM, Meyer CR, Koeppe RA, Stohler CS (2001) Regional mu opioid receptor regulation of sensory and affective dimensions of pain. Science 293:311–315.

Zubieta JK, Ketter TA, Bueller JA, Xu Y, Kilbourn MR, Young EA, Koeppe RA (2003) Regulation of human affective responses by anterior cingulate and limbic mu-opioid neurotransmission. Arch Gen Psychiatry 60:1145–1153.

Workshop

Fibromyalgia Syndrome

PHILIP MEASE, LESLEY M. ARNOLD, ROBERT BENNETT, ANNELIES BOONEN, DAN BUSKILA, SERENA CARVILLE, AMY CHAPPELL, ERNEST CHOY, DANIEL CLAUW, DINA DADABHOY, MICHAEL GENDREAU, DON GOLDENBERG, GEOFFREY LITTLEJOHN, SUSAN MARTIN, PHILIP PERERA, I. JON RUSSELL, LEE SIMON, MICHAEL SPAETH, DAVID WILLIAMS, and LESLIE CROFFORD

ABSTRACT. The fibromyalgia syndrome (FM) workshop at OMERACT 8 continued the work initiated in the first FM workshop at OMERACT 7 in 2004. The principal objectives were to work toward consensus on core domains for assessment in FM studies, evaluate the performance quality of outcome measures used in a review of recent trials in FM, and discuss the research agenda of the FM working group. An initiative to include the patient perspective on identification and prioritization of domains, consisting of focus groups and a patient Delphi exercise, was completed prior to OMERACT 8. Patient-identified domains were, for the most part, similar to those identified by clinician-investigators in terms of symptoms and relative importance. However, patients identified certain domains, such as stiffness, that were not included by physicians, and emphasized the importance of domains such as dyscognition and impaired motivation. Many of the principal domains agreed upon by the clinician-investigators, patients, and OMERACT participants, including pain, fatigue, sleep, mood, and global measures, have been used in clinical trials and performed well when viewed through the OMERACT filter. The research agenda items reviewed and approved for continued study included development of objective "biomarkers" in FM, development of a responder index for FM, and coordination with the WHO's International Classification of Functioning Disability and Health (ICF) Research Branch and the US National Institutes of Health's Patient Reported Outcome Measures Information System network (PROMIS) to develop improved measures of function, quality of life, and participation. The OMERACT process has provided a framework for identification of key domains to be assessed and a path toward validation and standardization of outcome measures for clinical trials in FM. (J Rheumatol 2007;34:1415–25)

Key Indexing Terms:
FIBROMYALGIA OMERACT OUTCOME MEASURES PAIN

Fibromyalgia syndrome (FM) as defined by the American College of Rheumatology 1990 definition for clinical trials is a chronic widespread pain condition with characteristic tender points on physical examination, often associated with a constellation of symptoms such as fatigue, sleep disturbance, headache, irritable bowel syndrome, and mood disorders[1]. Whereas surveys in the United Kingdom have identified the phenomenon of "chronic widespread pain" in up to 11% of the population at any given time[2], epidemiologic work in the US suggests that FM, when including the requisite tender

Supported by a grant from Pfizer Global Research and Development, Ann Arbor, Michigan, USA, for the patient focus groups and Delphi exercise.

P.J. Mease, MD, Seattle Rheumatology Associates, Chief, Division of Rheumatology Research, Swedish Medical Center, Clinical Professor of Medicine, University of Washington, Seattle, WA; L.M. Arnold, Associate Professor, Director, Women's Health Research Program, Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati, OH; R. Bennett, Professor of Medicine and Nursing Research, Oregon Health & Science University, Portland, OR, USA; A. Boonen, PhD, Department of Internal Medicine, Division of Rheumatology, University Hospital Maastricht and Caphri Research Institute, University of Maastricht, Maastricht, The Netherlands; D. Buskila, Department of Medicine H, Soroka Medical Center, Beer Sheva, Israel; S. Carville, Sir Alfred Baring Garrod Clinical Trials Unit, Department of Academic Rheumatology, King's College London, London, UK; A. Chappell, Medical Fellow, Eli Lilly and Company, Indianapolis, IN, USA; E. Choy, Sir Alfred Baring Garrod Clinical Trials Unit, Department of Academic Rheumatology, King's College London, London, UK; D. Clauw, Professor of Medicine and Psychiatry, University of Michigan, Ann Arbor, MI; D. Dadabhoy, Clinical Lecturer, Division of Rheumatology, University of Michigan, Ann Arbor, MI; R.M. Gendreau, Chief Medical Officer, Cypress Bioscience, Inc., San Diego, CA; D. Goldenberg, Chief, Rheumatology, Newton-Wellesley Hospital, Professor of Medicine, Tufts University School of Medicine, Newton, MA, USA; G. Littlejohn, Director of Rheumatology, Monash Medical Centre, Associate Professor, Monash University, Melbourne, Australia; S. Martin, Director, Outcomes Research, Pfizer, Ann Arbor, MI; P. Perera, Chief Medical Officer, Vice-President of Clinical Research, Jazz Pharmaceuticals, Palo Alto, CA; I.J. Russell, Associate Professor of Medicine, Director, University Clinical Research Center, The University of Texas Health Science Center at San Antonio, San Antonio, TX; L. Simon, Associate Clinical Professor of Medicine, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA, USA; M. Spaeth, Friedrich-Baur-Institut, University of Munich, Munich, Germany; D.A. Williams, Associate Professor, Rheumatology/Internal Medicine, University of Michigan, Ann Arbor, MI; L. Crofford, Gloria W. Singletary Professor of Internal Medicine, Chief, Division of Rheumatology and Women's Health, University of Kentucky, Lexington, KY, USA.

Address reprint requests to Dr. P.J. Mease, Seattle Rheumatology Associates, 1101 Madison, Suite 1000, Seattle, WA 98104. E-mail: pmease@nwlink.com

point count, is present in 2% of the adult population (3.4% of the female population)[3]. A prevailing theory of pathogenesis is dysregulation of pain pathways leading to central sensitization and marked by neurotransmitter, neurohormone, and sleep physiology irregularities[4-8]. Uncertainties regarding pathophysiology and absence of validated objective markers of disease activity limit progress in therapeutic approaches to FM.

The treatment of FM has included both nonpharmacologic therapies such as exercise, massage, cognitive behavioral therapy, and others, and pharmacologic therapies, which primarily affect neurophysiologic function, often in a variety of combinations. These include medications traditionally used as antidepressants, analgesics, muscle relaxants, antiepileptics, and others[7,9-14].

There is currently no therapy formally approved by the European Agency for the Evaluation of Medicinal Products or the US Food and Drug Administration for the pain of FM or the syndrome as a whole. Because there have been virtually no standardized or validated outcome measures for FM, there has been uncertainty about which key domains of the condition should be measured and whether measures for pain, sleep, fatigue, or other symptoms used elsewhere in clinical research would be applicable in FM. Other key research problems have included the influence of comorbid psychiatric conditions, gender, disability, and other factors on outcomes. Yet another problem has been how to effectively demonstrate improvement of multidimensional function as well as pain. Despite these uncertainties, a number of large controlled trials have been conducted in FM in recent years, comprising analgesics, antiepileptics, drugs that augment serotonin and norepinephrine function, and components that modulate sleep, to name a few, and which have effectively distinguished placebo and treatment response in domains such as pain, fatigue, sleep, and function[7,9-12]. Given this success and the large unmet need to have approved therapies for FM, a group of FM clinician-investigators and industry researchers met to try to achieve consensus on a set of core domains to be assessed in clinical trials and evaluate the quality of outcome measures used to assess those domains so that they may be validated in FM. These, in turn, will be helpful to regulatory agencies involved in approving emerging therapies for FM. The group conducted a workshop at OMERACT 7 in May 2004[15]. This work continued as a workshop at OMERACT 8.

Workshop Objectives and Intended Outcomes

The objectives of the FM workshop at OMERACT 8 were to further the work initiated at OMERACT 7[15] and achieve the following goals: (1) work toward consensus on the "core" domains to be assessed in FM clinical trials and longterm observational studies; (2) further evaluate the performance characteristics of outcome measures used to assess these domains in clinical trials; and (3) identify and frame, where possible with existing data, the ongoing research agenda of the workshop.

Methods

These objectives were accomplished in oral presentations reviewing work from the steering committee, in breakout groups that discussed the content of these presentations, in reports of group discussions to the workshop as a whole, and in voting on domains in the workshop and in the final plenary session. Preparatory work by members of the OMERACT FM steering committee was accomplished during the 2 years since OMERACT 7 in committees focused on domains and outcome measures. Following the clinician-investigator Delphi conducted prior to OMERACT 7, the domain work was advanced by patient focus groups and a subsequent patient Delphi. The committee members also conducted a literature review of all therapy trials in FM, an up to date summary of the performance characteristics of measures used in recent clinical trials in FM, and a focused review of objective biomarker data in FM. Other items on the research agenda undertaken by the steering committee, as reported in the workshop, included development of a composite responder index for FM and improved patient-reported measures of function, quality of life, and participation, being developed in conjunction with the NIH-PROMIS network and the WHO ICF Research Branch.

Domains of Assessment in FM (L.M. Arnold, R. Bennett, D. Clauw, L. Crofford, D. Goldenberg, S. Martin, P. Mease, I.J. Russell, D. Williams)

Several steps have been taken to establish a prioritized set of domains of FM from which a core set recommended to be investigated in clinical studies can be established. Prior to OMERACT 7, the steering group identified a group of domains that were prioritized in a Delphi exercise among FM clinician-investigators and formed the basis for discussion and voting at the OMERACT 7 workshop (see below). It was also recommended that the perspective of patients on important domains be obtained and integrated in deliberations on the core set. A series of patient focus groups were held, followed by a patient Delphi exercise (see below). The results of both Delphi exercises were presented at the OMERACT 8 FM workshop and in the review of the workshop in the final plenary session of OMERACT 8. Voting occurred in both settings, the objective being to provide guidance to the steering group regarding further development of a finalized core set.

Clinician-investigator Delphi. Prior to OMERACT 7, the FM workshop steering group developed a set of 40 potential domains of assessment for FM clinical trials. Between December 2003 and April 2004, fifty-one FM experts were approached to participate in a Delphi exercise to prioritize these domains, and 23 completed 3 rounds of this exercise. A Delphi exercise was felt to be a good method to derive expert opinion[16-19]. The results of this process were presented at OMERACT 7, followed by a presentation of clinical trial results and breakout discussions, with subsequent voting on domain prioritization. Table 1 shows the most highly prioritized domains of the Delphi exercise and the OMERACT 7 voting[15].

Table 1. Comparison of pre-OMERACT 7 Delphi scores and OMERACT 7 ratings. A. Median scores (points assigned out of 100 possible) for the top 12 domains identified by FMS clinician-investigators in a Delphi exercise conducted prior to OMERACT 7. B. Percentage of OMERACT 7 attendees who agreed these domains were essential to assess in clinical trials of FMS (with addition of "Multidimensional function").

A

Domain	Median Delphi Score
Pain	16
Fatigue	10
Patient global	10
Sleep quality	8
Health related quality of life	5
Physical function	5
Treatment side effects	5
Depression	5
Tender point intensity	2
Dyscognition	2
Anxiety	2
Clinican global	1

B

Domain	OMERACT 7 Participants,%
Pain	100
Patient global	94
Fatigue	85
Health related quality of life	76
Multidimensional function	75
Sleep quality	70
Depression	65
Treatment side effects	58
Physical function	42
Tender point intensity	18
Dyscognition	21
Anxiety	21
Clinican global	23

In general, there was considerable consensus between the clinician-investigators who participated in the Delphi and the OMERACT group as a whole. The OMERACT group discussion included focus on the importance of assessment of multidimensional aspects of function, which is being addressed in the research agenda by liaison with the WHO-ICF and NIH-PROMIS groups. It was also agreed that it would be optimal to include the patient perspective in development of consensus on the core domains of assessment. To this end, patient focus groups have been conducted and a patient Delphi was performed prior to OMERACT 8.

Patient focus groups on FM domains. The initial stage of gaining a patient perspective on FM domains involved patients from Cincinnati, Ohio (L.M. Arnold), Ann Arbor, Michigan (L.J. Crofford) and Seattle, Washington (P. Mease). In each of the 3 centers 2 focus groups of 7–10 FM patients [n = 48 total fulfilling American College of Rheumatology (ACR) criteria] were conducted by group moderators from MAPI Values, an outcomes research organization (made possible by a grant from Pfizer Global Research and Development, Ann Arbor, MI). The focus groups were conducted between July 2004 and September 2004. As part of the discussion, patients were asked to identify their FM symptoms and describe how FM affected important areas of functioning. They were asked to indicate the symptoms or impairment that they would most like treatment to improve. The focus groups were audiotaped and transcribed for analysis. All identifying information was removed from the transcripts. A detailed description of the process and outcome of the focus groups will be published separately.

The patients identified pain as a key domain, as well as fatigue and disturbed sleep. Other important domains included depression, cognitive impairment (decreased concentration, disorganization, memory problems), and social and occupational dysfunction. Notably, the domains identified by the patients are generally consistent with several of the important domains identified by clinician-investigators in the previously described Delphi exercise. The patient findings also underscored the need to assess multidimensional aspects of function, as recommended by OMERACT 7 workshop attendees.

Patient ratings of FM domains. The focus groups provided qualitative information on important FM domains. To develop a more quantitative, reliable, and valid determination of patient consensus about the relative priority of different domains of FM, a patient Delphi exercise was conducted using data from the focus group discussions to generate the domain list. In addition to Seattle, Cincinnati, and Ann Arbor (D. Clauw, D.A. Williams) 2 sites were added, Lexington, Kentucky (L.J. Crofford) and San Antonio, Texas (I.J. Russell), the latter to include Hispanic patients in the study. Among the 5 centers, a total of 100 patients participated (20 at each site). The patient Delphi exercise was conducted between September 2005 and May 2006.

Patient Delphi. Of 100 patients participating in 5 centers, 86 took part through the second round of the 2-round Delphi exercise. Patients were presented the list of 40 FM domains distilled as most important from the focus groups and using language derived from transcripts of the focus groups. They were asked to award 100 points among these domains, based upon their judgment about the individual importance of the domain. After the first round results were tallied, each patient was re-presented with their first-round scoring, the mean

score of the whole group for each domain, and the minimum and maximum score. They were then allowed to reflect on their original response and re-respond, either by keeping their original score or changing it, if their review of others' responses led them to do so. The top-rated domains from the second round are presented in Table 2. A detailed description of the patient Delphi process and a variety of subanalyses will be provided separately.

The results of the patient Delphi exercise were, for the most part, similar to the results of the clinician-investigator Delphi. The domain of pain was ranked most highly in both, including the varied ways that patients described pain in the focus group discussions. Other domains ranked similarly highly included fatigue, sleep disturbance, multidimensional function, depression as a comorbid problem, and cognitive difficulty. This last domain was summarized in one word in the clinical-investigator Delphi, "dyscognition," whereas it was described in a variety of ways by patients, including "problems with attention or concentration," "disorganized thinking," and "memory problems." Aspects of function important to patients included the influence of the illness on making plans and accomplishing goals and tasks, including routine activities of daily living, as well as the motivation to accomplish things. Patients did not articulate phrases such as "patient global" or "health related quality of life" that would subsume a variety of domains that affect their overall sense of well-being, nor were they focused on treatment side effects as an important domain to measure in clinical trials. One domain ranked highly by patients but not by clinician-investigators was "stiffness." In breakout groups, patients described this as an important symptom. It is not described in the same way as the stiffness of rheumatoid arthritis but appears to have a different quality. It was felt that this deserved further research on how best to assess.

Review of Treatment Trials in FM and Assessment of Outcome Measures (S. Carville, A. Chappell, E. Choy, R.M. Gendreau, S. Martin, P. Perera)

The OMERACT workshop steering group and a multidisciplinary EULAR FM task force are working in collaboration to do a systematic review of all treatment trials of FM and assess the performance of outcome measures used in those trials. The members of the OMERACT workshop steering committee are noted above, representing 6 countries, consisting of rheumatologists, a psychiatrist, a psychologist, and a physiologist. The EULAR task force consists of rheumatologists, pain spe-

Table 2. Comparison of OMERACT 7 voting and patient Delphi: key domains. A. OMERACT 7 voting: FMS domains ranked as most important in clinician-investigator Delphi exercise performed prior to OMERACT 7. Percentage column shows percentage of OMERACT 7 attendees who agreed that these domains were essential to assess in FMS clinical trials. B. Patient Delphi: mean scores (points assigned out of 100 possible) for the top 14 domains identified by patients as important in FMS. Percentage column reflects percentage of patients who felt domains should be assessed.

A. OMERACT 7 Voting		**B.** Patient Delphi	
Domain	%	Domain/Item	Mean (%)
Pain	100	Pain or physical discomfort	6.9 (95)
Patient global	94	Joints aching or pain	5.7 (90)
Fatigue	85	Lack of energy or fatigue	5.5 (96)
HRQOL	76	Effect on sleep (difficulty falling asleep, staying asleep, or getting up in the morning)	5.3 (92)
Multidimensional function	75	Problems with attention or concentration (difficulty concentrating on things, difficulty thinking, "fibro-fog")	4.7 (91)
Sleep	70	Stiffness	4.2 (91)
Depression	65	Disorganized thinking (difficulty in expressing yourself, difficulty in answering questions quickly, or difficulty making plans)	3.6 (85)
Treatment side effects	58	Difficulty moving, walking, or exercising	3.5 (86)
Physical function	42	Having to push yourself to do things	3.1 (83)
Clinical global	23	Effect on ability to make plans, accomplish goals, or complete tasks	3.0 (79)
Tender point intensity	21	Feeling tender where touched	3.0 (77)
Dyscognition	21	Depression (disappointed, sad, resigned, or unmotivated)	3.0 (74)
Anxiety	21	Affected/limited in doing normal daily life and household activities	2.8 (82)
		Memory problems	2.6 (81)

Table 3. Effect sizes observed in clinical trials of therapeutic agents in fibromyalgia.

Drug	Duration	Pain				Sleep	Fatigue		Mood		Global		Function
Outcome	No. of Studies	Pain VAS	SF-36 Bodily Pain	Tender Points	Morning Stiffness	Sleep	Fatigue	SF-36 Vitality	Mood Anxiety	Mood Depression	Patient Global	FIQ Total	SF-36 Physical Function
A*	1-8 weeks	0.45	0.39	0.29		0.73	0.33	0.31	0.26	0.23	0.48		0.27
B*	Average across 9 studies	0.52		0.29		0.66	0.45				0.66		
C*	1-12 weeks	0.95		0.48	0.52		0.57						
D*	1-12 weeks	0.35		0.44	0.32		0.02				0.29	0.19	
E*	1-12 weeks Dose A Dose B	 0.48 0.48		 0.41 0.29		 0.35 0.30				 0.15 0.25	 0.40 0.37	 0.50 0.46	
F§	1-12 weeks	0.39	0.39	0.22	0.32	0	0.13	0.15	0.27	0.13		0.37	0.33
G§	1-9 weeks	0.49		0.18								0.11	
H*	1-12 weeks	0.53	0.35		0.73	0.27	0.09	0.05	0.25	0.40	0.50	0.27	0.40
I§	1-9 months			(count) 0.6								0.6	
J§	1-14 weeks	1.48		0.50			0.79		0.23	0.44	1.26	1.00	(M-HAQ) 0.49
K*	1-8 weeks Dose A Dose B	 0.38 0.38	 0.51 0.51	 0.34 0.35	 0.54 0.55	 0.57 0.56	 0.58 0.53	 0.28 0.05	 0.09 0.01	 0.13 0.19		 0.51 0.43	 0.42 0.28
OMERACT filter	Truth											✓	
	Discrimination	Medium to high	Medium	Small to medium	Small to medium	Medium	Medium	Small	Small	Small	Medium	Small to medium	Small
	Feasibility	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Truth: ✓ indicates instrument has been validated in FMS. Only the Fibromyalgia Impact Questionnaire (FIQ) has been formally validated in FMS; other measures are in process of being validated. Discrimination: indicates sensitivity to change assessed by effect size (0.2-0.49 = small, 0.5-0.79 = medium, > 0.8 = large). Feasibility: ✓ indicates instrument is feasible as it has been used in FMS clinical trials.

* Effect size calculated using the following method: difference in mean endpoint score divided by pooled SD of the change. § Effect size calculated using the following method: difference in mean endpoint score divided by baseline SD.

cialists, experts in rehabilitation, a neurologist, an occupational therapist, a bio-scientist, psychiatrist, epidemiologist, and a patient representing 11 European countries. The group at OMERACT 7 reviewed several recent pharmaceutical clinical trials and developed a table of effect sizes seen in various domains (Table 3)[9,17,20-26]. This was updated for OMERACT 8 with data from recent trials of pramipexole, duloxetine, and sodium oxybate. The EULAR task force has conducted a systematic review of Medline, Pubmed, EmBASE, CINAHL, PsycINFO, Web of Science, Science Citation Indices, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews with the keywords "fibromyalgia," "treatment or management," and "trial," including both pharmacological and nonpharmacological interventions. Studies were excluded if they did not utilize the ACR classification criteria, were not clinical trials, or included patients with chronic fatigue syndrome or myalgic encephalomyelitis. Most of these have been reviewed[9,27-33] (see Table 4 for a summary of studies). From the 162 selected trials, where possible, data were extracted on sample size, randomization, blinding, duration of disease, duration of treatment, and change in pain assessed by visual analog scale (VAS) and Fibromyalgia Impact Questionnaire values, other outcome measures, instruments used, and change values

Table 4. Studies identified in the systematic review.

Class of treatment	Studies
Selective serotonin reuptake inhibitors	Anderberg 2000, Arnold 2002, Nørregaard 1995, Kee 2004
Tricyclic antidepressants	Carrette 1994 & 1995, Ginsberg 1996, Heymann 2001, Capaci 2002, Goldenberg 1996, Giordano 1999, Hannonen 1998
Dual reuptake inhibitors	Arnold 2004 & 2005, Nagaoka 2004, Vitton 2004, Sayar 2003,
5HT2/3 antagonists	Fäber 2000, Haus 2000, Hrycaj 1996, Müller 2000, Olin 1998, Samborski 2006, 2004a, 2004b, Späth 2004, Stratz 2000
Monoamine oxidase inhibitors	Hannonen 1998, Ginsberg 1998, Nicoledi 1996, Yavuzer 1998
Systemic analgesics	Graven-Neilsen 2000, McLean 2000, Raphael 2002, Russell 2000, Sörensen 1995, Bennett 2003
Topical analgesics	Scudds 1995, Janzen 1997, McCarty 1994
Tri-iodothyronine	Lowe 1997a, b, c
Individual pharmacological interventions	Paulson 1996, Aspergen Kendall 2004, Bessette 1998, Citera 2000, McLain 2002, Moldofsky 1996, Quijada-Carrera 1996, Rico-Villademoros 2005, Russell 1995, Scharf 2003, Volkmann 1997, Crofford 2005, Bennett 1998, Teitelbaum 2001, Holman 2005, Finckh 2005, Wood 2005
Aerobic exercise	Mengshoel et al. 1992, Nørregaard 1997, Nichols et al. 1994, Ramsay et al. 2000, Schachter et al. 2003, Richards et al. 2003, Gowans et al. 2001, Van Santen et al. 2002 a&b, Meyer et al. 2000, Da Costa et al. 2005
Strength training	Dupree Jones 2002, Häkkinen 2005, Geel 2002, Kingsley 2005
Mixed exercise	Bailey 1999, Dawson 2003, Isomeri 1993, Martin 1996
Pool-based	Altan 2004, Jentoft 2001
Dietary interventions	Bramwell 2000, Edwards 2000, Azad 2000, Kaartinen 2000, Merchant 2000, Deuster 1998, Merchant 2001
CBT	Neilson 1992, Singh 1998
CBT & exercise	Rivera-Redondo 2004, Mason 1998, Soares 2002, Goldenberg 1994, Mengshoel 1995
Education	Fors 2000, Oliver 2001, Nicassio 1997, Vlaeyen 1996
Education & exercise	Cedraschi 2003, Burkhardt 1994, King 2002, Gowans 1999, Mannerkorpi 2000, Zijlstra 2005, Lemstra 2005, Bailey 1999
Balneotherapy	Evick 2002, Yurtkuran 1996, Günther 1994, Zjilstra 2005
Homeopathy	Bell 2004a, b, c
Physiotherapy related	Brattberg 1999, Blunt 1997, Hains 2000, Field 2003
Meditation	Kaplan 1993, Astin 2003
Laser/light	Gür 2002, Pearl 1996
Acupuncture	Sprott 1998, Deluze 1992, Assefi 2005, Harris 2005
Magnets	Colbert 1999, Alfano 2001
Other nonpharmacological interventions	Almeida 2003, Alamo 2002, Chesky 1997, Huuhka 2004, Meuller 2001, Kendall 2000, Sverdrup 2004, Fors 2002, Bosch-Romero 2002, Theime 2003, Broderick 2005, Luckazer 2005, Biasi 1999, Keel 1998, Bennett 1996, Pfeiffer 2003, Creamer 2000, Worrell 2001

where available. The data extraction was verified by a second committee member.

There is an opportunity to synergize the work already carried out by the EULAR working group with the ongoing effort of the OMERACT working group. The OMERACT working group on FM has established key domains that should be assessed in randomized controlled trials, and will continue to report effect sizes for assessments in the available major FM studies (Table 3). Each outcome measure collected in the EULAR database can be mapped to a specific OMERACT domain. Outcome measures that have already been used in randomized controlled trials (RCT) are likely to be feasible and face-valid. Calculating their effect size (changes before and after treatment) assesses their sensitivity to change. Therefore data from the EULAR database as well as any available study results fulfilling the quality criteria as of April 2006 can establish whether there is any particular outcome instrument in each of the OMERACT FM domains that fulfils the 3 key aspects of the OMERACT filter, truth, discrimination, and feasibility. The work can be extended to determine the minimum clinically important difference for each selected outcome measure and contributes further to the development of a set of response criteria for FM.

This review revealed that for each of the key OMERACT domains, there are instruments that have been used in clinical trials. Many of these have been evaluated for validity and are feasible and sensitive to change in FM. Sleep is the one key OMERACT domain that lacks a sensitive measure in the systematic review, but in recent RCT, the Jenkins Sleep Questionnaire and the Medical Outcomes Study Sleep Scale performed well.

Research Agenda: Objective Measures in FM (D. Clauw, L.J. Crofford, D. Dadabhoy, I.J. Russell, M. Spaeth)

Evidence-based objective measures are valuable tools in clinical practice and research. Through a systematic review of the literature, potential biomarkers available for FM were evaluated. A summary of the various biomarkers was presented at OMERACT 8. Each objective measure was rated for category (clinical or research only) and for the strength and consistency of evidence supporting its use. The objective measures found to have the strongest evidence are described and summarized below. A detailed list of the primary articles reviewed for OMERACT 8 will be noted in an upcoming report on objective measures in FM.

Evoked potentials. Auditory, somatosensory, and visual evoked potential studies were reviewed. Reduced P300 amplitude during auditory discriminated task paradigm is the biomarker with the strongest current evidence of the evoked potentials[34]. Observed in 3 cross-sectional studies by 2 different groups, the reduced P300 amplitude measure appears promising, but larger studies by different groups with attention to standardizing methods are warranted. Currently, there are few and varied studies that evaluated somatosensory and visual evoked potentials, and the findings were inconsistent.

Neural imaging. The primary modes of imaging used in FM include functional magnetic resonance imaging (fMRI), single-photon emission computed tomography (SPECT), and positron emission tomography (PET). fMRI studies evaluating pain processing have the strongest current evidence of the neural imaging studies. Specifically, quantitative sensory activation of neural pain processing areas (SII, insula, ACC) has been noted in 5 cross-sectional studies by 2 different groups[35]. Notably, affected areas have been shown on imaging to be influenced by cognitive factors such as catastrophizing. In summary, the advantages of fMRI include the modality being less invasive and having high temporal and spatial resolutions. Disadvantages include cost and practicability as well as the inability to perform receptor-ligand studies, as can be performed in PET and SPECT.

Autoantibodies. The practicality of a blood test result that can be used as an objective marker makes this group of measures more attractive. Certain autoantibodies (e.g., antiserotonin, antiganglioside, antiphospholipid antibody) have been shown to be different in patients and controls, but the generalizability and sensitivity/specificity of these findings are not clear[36]. In chronic fatigue syndrome, investigators have noted a shift from a T1 to T2 immune response that may account for the increased production of nonspecific autoantibodies. As such, increases in concentrations of nearly any antibody may be seen in this spectrum of illness, and any autoantibody that would be considered for use as a diagnostic marker will require stringent controls to ensure its validity in this setting.

Genetics. Genetic studies have generally yielded noninformative or inconsistent results. Of the genetic markers, COMT haplotype and HLA linkage, reviewed in one study each, have shown an association[37].

Hypopituitary-adrenal axis. In basal and diurnal cortisol studies, the measure found most consistently was a flattened diurnal plasma cortisol with elevated trough, found in 3 of 4 cross-sectional studies by 2 of 3 groups[38]. Studies evaluating basal plasma cortisol, salivary basal and diurnal cortisol, and urinary cortisol have shown inconsistent results, but generally demonstrate normal to reduced basal levels. Since atypical depression can show reduced cortisol, biopsychological factors that influence cortisol levels may be contributing to the inconsistent results currently reported. In addition, studies have suggested that the presence of comorbid posttraumatic stress disorder and of early childhood abuse may dramatically affect these results and have been a confounder in previous studies. These factors need to be better elucidated and accounted for in future studies.

Biochemicals. There is significant evidence that elevated substance P in cerebrospinal fluid (CSF) is a reproducible marker of a number of different chronic pain states[39]. In contrast, normal substance P has been noted in chronic fatigue syndrome[40]. Difficulty in obtaining the measure (i.e., from the CSF) limits its clinical use.

The amino acid tryptophan, the cytokine interleukin 8, and the beta-adrenergic G-couple protein receptors all have been shown to be different in patients compared to controls in a couple of studies, but none was evaluated in longitudinal studies or by different groups[39,41,42].

Psychophysical testing. Psychophysical pain testing (sometimes referred to as quantitative sensory testing) is the best supported objective measure currently in the literature. Use of pressure pain thresholds, heat pain threshold, and tender point intensity/index is well established to differentiate patient groups from controls. The clinically used tests of pain thresholds, i.e., by tender point counts or dolorimetry, have been shown to be marginally biased, however, by cognitive and psychological factors (i.e., expectancy). These biases may be minimized by more sophisticated paradigms, but they are more difficult to use in routine clinical practice[43]. Studies suggest that pressure pain thresholds are more closely related to clinical pain reports than heat pain thresholds.

Diminished diffuse noxious inhibitory controls (DNIC) is a more recently investigated type of psychophysical study that has been noted in FM in 4 cross-sectional studies by different groups that used variable test and conditioning stimuli[44]. This suggests a defect in normal descending inhibitory pain signals in FM may be partly responsible for the augmented pain processing noted in these patients. Diminished DNIC have also been noted in other types of chronic pain, i.e., temporomandibular and hip osteoarthritis[45]. The normalization of DNIC after hip osteoarthritis surgery suggests that it may be an objective measure of chronic pain.

Muscle. Despite the interest in and investigation for objective peripheral muscle abnormalities, the results have remained variable and have not yet been reproduced by different groups. Additionally, there is great heterogeneity in the methods in evaluating for objective muscle abnormalities. To identify possibly useful objective measures, further investigations are necessary, preferably utilizing noninvasive procedures.

Autonomic reactivity. Tilt-table testing and heart rate variability were evaluated. The consistent and reproducible finding of lower heart rate variability in FM compared to controls (3 cross-sectional studies by 2 different groups) makes it a more useful measure than tilt-table testing[46]. Findings also suggest that aberrations in heart rate variability may predispose to FM symptoms[47]. Longitudinal studies evaluating change over time in autonomic reactivity would be useful.

Sleep and activity. In addition to sleep logs, polysomnography has consistently confirmed patient reports of hypersomnolence[48]. Actigraphy, although less intrusive, does not appear to be as sensitive a marker, but further investigation will be necessary.

In summary, except for psychophysical testing, no objective measure has been appropriately evaluated and shown to improve with improvements in clinical status in a longitudinal study (type I evidence). OMERACT will work toward a consensus on promising objective measures to be used in research and clinical arenas. An effort by different groups to systematically evaluate these measures in research trials to obtain useful, comparable results will be vital for progress in outcome research.

Currently, a metaanalysis of the data available on objective biomarkers is not warranted — the different studies are too dissimilar. Most biomarkers have too few reports with a small number of subjects. There is a need to identify biomarkers for future studies that have reproducibility and predictive value, practicability, and biological and temporal relevance in FM.

Research Agenda: Responder Index (L.M. Arnold, D. Clauw, L.J. Crofford, P. Mease, D. Goldenberg, D.A. Williams)

Once there is consensus about important domains, we will assess data from FM studies of pregabalin[24], duloxetine[21], milnacipran[26], and gabapentin (in progress) in FM that have utilized outcome measures for the domains of interest, as done during development of the core set of outcome measures for the ACR20[49,50]. We will use the criteria for selection of clinical trial outcome measures adopted by OMERACT as the OMERACT filter originally proposed by Tugwell and Bombardier[51].

Next, adopting the approach used to develop the ACR20[50] and the EULAR Response Criteria[52], we will use the core set of outcome measures identified by the above procedures and test several different definitions of FM state and improvement in a 3-step process:

Step 1. We will conduct a survey of 500 clinicians with extensive experience in treatment of FM. These clinicians will be drawn from members of the ACR and the International Myopain Society. From this pool, we estimate a 20% response rate to reach our goal of 100 respondents. Each will be presented with 10–12 sets of criteria for FM state and improvement constructed to have high face validity (based on consensus of the clinical investigators and consultants). Surveyed clinicians will rank the sets with respect to their perceived value in discriminating improved from non-improved patients.

Step 2. We will use clinical trial data from the pregabalin, duloxetine, milnacipran, and gabapentin trials to test the definitions of FM state and improvement.

Step 3. We will identify which improvement definitions characterize fewest placebo patients as improved.

We plan to include only data from studies of pharmacological agents because inclusion of data from behavioral or alternative medicine trials might add variance to the results, which might diminish the value of the responder index in large studies of the efficacy of pharmacological agents. Further, the responder indices such as the ACR20 are not used to evaluate treatment effects in studies of psychosocial interventions for patients with rheumatoid arthritis, because these interventions are not necessarily expected to produce outcomes similar to those produced by pharmacological agents. Thus, we propose to focus the development of the responder index for use in

pharmacological trials. Future studies could evaluate a responder index in nonpharmacological trials.

Research Agenda: Assessment of Multidimensional Aspects of Function, Quality of Life, and Participation in FM (A. Boonen, P. Mease, D.A. Williams)

Annelies Boonen and Alarcon Cieza are serving as liaison to the WHO-ICF (Research Branch) rheumatology working group, led by Gerold Stucki, and Dave Williams as liaison to the NIH-PROMIS network. The OMERACT FM group will participate in development of an ICF core set for FM, based on work done on the ICF in chronic widespread pain[53]. This process is being informed by the Delphi exercises on domains and contributes to the selection or development of measures to assess the "multidimensional function" domain, especially with regard to which subdomains must be included in such measures.

Existing outcome measures for FM have been criticized for having poor psychometric properties such as limited dynamic range (e.g., ceiling/floor effects), limited sensitivity to change over time, and inability to directly compare the effectiveness of differing interventions across multiple domains of meaningful clinical variables. Newer approaches to patient-reported outcomes depart from classical test construction by using item-response theory in combination with computer adaptive testing (IRT/CAT). This approach requires the development of large pools of well characterized test items, and uses computer algorithms to present the smallest number of items that will produce the most valid assessment of a particular outcome domain for a given patient[54-56]. The advantage of this approach is that a common assessment strategy can be used for each outcome domain of interest, it involves low patient burden, and it possesses superior measurement characteristics. David Williams is collaborating with the larger NIH/PROMIS project to develop refinements to the generic chronic illness assessment tool that can be applied specifically to FM.

Voting in Workshop and Plenary at OMERACT 8

After discussion on these domains, outcome measures, and research agenda items in breakout groups that included members of OMERACT and patients with rheumatoid arthritis, psoriatic arthritis, and FM, the workshop members voted on the question of whether a domain should be part of the core set in FM clinical trials and longitudinal studies. They could choose either "yes" or "no" on whether the domain was essential to be assessed in a study or was optional and should be in the research agenda regarding its importance to be measured and needing further development of adequate assessment instruments. This decision may have been influenced by both the relative importance of the domain and the current adequacy of instruments to assess the domain (Table 5).

In the final plenary session of OMERACT 8, the workshop proceedings were summarized and further voting by the whole OMERACT 8 group took place. In this session, it was decided there would be 3 choices: (1) Is the domain "essential" to include in all studies; (2) Is the domain important to measure but not necessarily mandatory for all types of studies; or (3) Is the domain of uncertain importance to include in the core set, does it need clarification, or does it clearly not have adequate outcome measures such that it should be in the research agenda. Because information and evidence about the domains and outcome measures were not presented to the group as a whole (as might occur in a plenary module), this vote was understood to be used as guidance and not as a formal consensus. Table 6 shows the results of the voting in the workshop and plenary sessions.

Table 5. Workshop group responses (n = 37).

Domain	% of Positive Votes*
Pain	100
Fatigue	94
Patient global	94
Multidimensional function	86
Tenderness	74
Sleep	66
HRQOL	65
Dyscognition	61
Stiffness	60
Depression	47
Anxiety	47
Treatment side effects	38

*Percentage of FM workshop attendees who thought the domains identified in prior OMERACT 7 Delphi workshop and patient Delphi were essential to assess in clinical trials of FMS.

It is clear that the key domains of FM to be investigated in studies, domains endorsed by both clinician-investigators (as reviewed in OMERACT 7) and patients, include pain, fatigue, sleep disturbance, multidimensional function, quality of life, mood disorders, and cognitive dysfunction. An additional domain highlighted by patients is stiffness. As well, an important domain to assess in a trial of a medication would be treatment side effects, to determine the tradeoff with potential benefit. Not all these domains are considered essential in all studies. For example, cognitive dysfunction, anxiety, and stiffness may not be "core" enough or there may be uncertainty about how best to measure these domains, such that there would be merit in including their assessment, but it would not be essential to measure these domains in all trials.

Conclusions

Since OMERACT 7, there has been an advance in our understanding of important symptom domains in FM and additional data on instruments used to assess these symptom domains. It has been shown consistently that pain is the principal symptom to be measured, and good effect sizes have been demon-

Table 6. Full OMERACT 8 group responses (n = 104). All numbers are expressed as percentages of all persons attending final OMERACT plenary session. Column A: Essential for core set for all clinical studies. Column B: Necessary but not mandatory for all clinical studies. Column C: Research agenda (implying more research needed to define the domain in the context of FMS)

Domain	A	B	C
Pain	94	3	3
Fatigue	86	13	1
Patient global	81	12	7
Sleep	64	256	10
Multidimensional function	60	28	12
HRQOL	52	34	14
Tenderness	50	27	24
Depression	44	34	21
Treatment side effects	40	34	26
Anxiety	2s	43	35
Dyscognition	21	42	37
Stiffness	13	35	52

strated with instruments to measure pain in FM clinical trials. Other important domains include fatigue and sleep disturbance. Measures of these domains show reasonable effect sizes in clinical trials. There is considerable overlap between the opinion of clinician-investigators and patients regarding the identification and prioritization of key domains to be assessed in FM. Domains such as stiffness, dyscognition, function, and motivation are clearly important to patients but have not been as reliably assessed. It is desirable to demonstrate that FM therapy can improve function, including physical, social, and occupational function. Effect sizes of available instruments to measure various dimensions of function are variable and tend to be small, which suggests either that function may not be as responsive as other clinical manifestations of FM over 8–12 weeks of treatment or that the measures are not sensitive enough to detect treatment effects. In collaboration with the WHO ICF and NIH PROMIS projects, work is under way to develop more specific and sensitive instruments to measure the various ways in which FM affects function, quality of life, and participation in meaningful activities and to demonstrate change with effective therapy. Similarly, it is difficult to assess and measure change in the subtle cognitive dysfunction expressed by many FM patients, a challenge that is on our current research agenda. As we gain a clearer understanding of the neuropathophysiology underlying FM, more objective biomarkers of disease activity may improve our ability to diagnose and assess therapeutic progress. Tracking the developments in this arena is also on the research agenda of the OMERACT working group. The ability to measure clinically meaningful change in multiple dimensions of FM utilizing a composite responder index is desirable; this too is on the research agenda. It is reassuring to note significant agreement between clinician-investigators' and patients' rankings of important symptom domains. Establishment of consensus about symptom domains and development of outcome measures for FM clinical trials are critical steps toward the identification of effective treatments for FM.

REFERENCES

1. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160-72.
2. Croft P, Rigby AS, Boswell R, et al. The prevalence of chronic widespread pain in the general population. J Rheumatol 1993;20:710-3.
3. Wolfe F, Ross K, Anderson J, et al. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995;38:19-28.
4. Bennett RM. Emerging concepts in the neurobiology of chronic pain: evidence of abnormal sensory processing in fibromyalgia. Mayo Clin Proc 1999;74:385-98.
5. Clauw DJ, Crofford LJ. Chronic widespread pain and fibromyalgia: what we know, and what we need to know. Best Pract Res Clin Rheumatol 2003;17:685-701.
6. Crofford LJ, Clauw DJ. Fibromyalgia: where are we a decade after the American College of Rheumatology classification criteria were developed? Arthritis Rheum 2002;46:1136-8.
7. Mease P. Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment. J Rheumatol 2005;32 Suppl 75:6-21.
8. Pillemer SR, Bradley LA, Crofford LJ, et al. The neuroscience and endocrinology of fibromyalgia. Arthritis Rheum 1997;40:1928-39.
9. Arnold LM, Keck PE Jr, Welge JA. Antidepressant treatment of fibromyalgia. A meta-analysis and review. Psychosomatics 2000;41:104-13.
10. Barkhuizen A. Rational and targeted pharmacologic treatment of fibromyalgia. Rheum Dis Clin North Am 2002;28:261-90.
11. Bennett RM. The rational management of fibromyalgia patients. Rheum Dis Clin North Am 2002;28:181-99.
12. Rao SG, Bennett RM. Pharmacological therapies in fibromyalgia. Best Pract Res Clin Rheumatol 2003;17:611-27.

13. Sprott H. What can rehabilitation interventions achieve in patients with primary fibromyalgia? Curr Opin Rheumatol 2003;15:145-50.
14. Williams DA. Psychological and behavioural therapies in fibromyalgia and related syndromes. Best Pract Res Clin Rheumatol 2003;17:649-65.
15. Mease PJ, Clauw DJ, Arnold LM, et al. Fibromyalgia syndrome. J Rheumatol 2005;32:2270-7.
16. Bennett RM. Disordered growth hormone secretion in fibromyalgia: a review of recent findings and a hypothesized etiology. Z Rheumatol 1998;57 Suppl 2:72-6.
17. Bennett RM, Kamin M, Karim R, et al. Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: a double-blind, randomized, placebo-controlled study. Am J Med 2003;114:537-45.
18. Gendreau M, Mease P, Rao S, et al. Milnacipran: A potential new treatment of fibromyalgia [abstract]. Arthritis Rheum 2003;48 Suppl:S616.
19. Rowe G, Wright G, Bolger F. Delphi. A reevaluation of research and theory. Technological Forecasting and Social Change 1991;39:235-51.
20. Arnold LM, Hess EV, Hudson JI, et al. A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. Am J Med 2002;112:191-7.
21. Arnold LM, Lu Y, Crofford LJ, et al. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. Arthritis Rheum 2004;50:2974-84.
22. Arnold LM, Rosen A, Pritchett YL, et al. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. Pain 2005;119:5-15.
23. Bennett RM, Clark SC, Walczyk J. A randomized, double-blind, placebo-controlled study of growth hormone in the treatment of fibromyalgia. Am J Med 1998;104:227-31.
24. Crofford LJ, Rowbotham MC, Mease PJ, et al. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52:1264-73.
25. Holman AJ, Myers RR. A randomized, double-blind, placebo-controlled trial of pramipexole, a dopamine agonist, in patients with fibromyalgia receiving concomitant medications. Arthritis Rheum 2005;52:2495-505.
26. Vitton O, Gendreau M, Gendreau J, et al. A double-blind placebo-controlled trial of milnacipran in the treatment of fibromyalgia. Hum Psychopharmacol 2004;19 Suppl 1:S27-35.
27. Adams N, Sim J. Rehabilitation approaches in fibromyalgia. Disabil Rehabil 2005;27:711-23.
28. Baker K, Barkhuizen A. Pharmacologic treatment of fibromyalgia. Curr Pain Headache Rep 2005;9:301-6.
29. Crofford LJ. Meta-analysis of antidepressants in fibromyalgia. Curr Rheumatol Rep 2001;3:115.
30. Crofford LJ, Appleton BE. The treatment of fibromyalgia: a review of clinical trials. Curr Rheumatol Rep 2000;2:101-3.
31. Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. JAMA 2004;292:2388-95.
32. Sim J, Adams N. Systematic review of randomized controlled trials of nonpharmacological interventions for fibromyalgia. Clin J Pain 2002;18:324-36.
33. Russell I, Kamin M, Bennett RM, et al. Efficacy of tramadol in treatment of pain in fibromyalgia. J Clin Rheumatol 2000;6:250-7.
34. Alanoglu E, Ulas UH, Ozdag F, et al. Auditory event-related brain potentials in fibromyalgia syndrome. Rheumatol Int 2005;25:345-9.
35. Giesecke T, Gracely RH, Williams DA, et al. The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort. Arthritis Rheum 2005;52:1577-84.
36. Klein R, Berg PA. High incidence of antibodies to 5-hydroxytryptamine, gangliosides and phospholipids in patients with chronic fatigue and fibromyalgia syndrome and their relatives: evidence for a clinical entity of both disorders. Eur J Med Res 1995;1:21-6.
37. Buskila D, Neumann L. Genetics of fibromyalgia. Curr Pain Headache Rep 2005;9:313-5.
38. Crofford LJ, Young EA, Engleberg NC, et al. Basal circadian and pulsatile ACTH and cortisol secretion in patients with fibromyalgia and/or chronic fatigue syndrome. Brain Behav Immun 2004;18:314-25.
39. Russell IJ. Advances in fibromyalgia: possible role for central neurochemicals. Am J Med Sci 1998;315:377-84.
40. Evengard B, Nilsson CG, Lindh G, et al. Chronic fatigue syndrome differs from fibromyalgia. No evidence for elevated substance P levels in cerebrospinal fluid of patients with chronic fatigue syndrome. Pain 1998;78:153-5.
41. Gur A, Karakoc M, Nas K, et al. Cytokines and depression in cases with fibromyalgia. J Rheumatol 2002;29:358-61.
42. Maekawa K, Twe C, Lotaif A, et al. Function of beta-adrenergic receptors on mononuclear cells in female patients with fibromyalgia. J Rheumatol 2003;30:364-8.
43. Petzke F, Clauw DJ, Ambrose K, et al. Increased pain sensitivity in fibromyalgia: effects of stimulus type and mode of presentation. Pain 2003;105:403-13.
44. Julien N, Goffaux P, Arsenault P, et al. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain 2005;114:295-302.
45. Kosek E, Ordeberg G. Lack of pressure pain modulation by heterotopic noxious conditioning stimulation in patients with painful osteoarthritis before, but not following, surgical pain relief. Pain 2000;88:69-78.
46. Buskila D, Press J. Neuroendocrine mechanisms in fibromyalgia-chronic fatigue. Best Pract Res Clin Rheumatol 2001;15:747-58.
47. Glass JM, Lyden AK, Petzke F, et al. The effect of brief exercise cessation on pain, fatigue, and mood symptom development in healthy, fit individuals. J Psychosom Res 2004;57:391-8.
48. Landis CA, Lentz MJ, Tsuji J, et al. Pain, psychological variables, sleep quality, and natural killer cell activity in midlife women with and without fibromyalgia. Brain Behav Immun 2004;18:304-13.
49. Felson DT, Anderson JJ, Boers M, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Arthritis Rheum 1993;36:729-40.
50. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727-35.
51. Tugwell P, Bombardier C. A methodologic framework for developing and selecting endpoints in clinical trials. J Rheumatol 1982;9:758-62.
52. van Gestel AM, Prevoo ML, van 't Hof MA, et al. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. Arthritis Rheum 1996;39:34-40.
53. Cieza A, Stucki G, Weigl M, et al. ICF Core Sets for chronic widespread pain. J Rehabil Med 2004;44 Suppl:63-8.
54. Cella D, Chang CH. A discussion of item response theory and its applications in health status assessment. Med Care 2000;38:II66-72.
55. Cook KF, O'Malley KJ, Roddey TS. Dynamic assessment of health outcomes: time to let the CAT out of the bag? Health Serv Res 2005;40:1694-711.
56. Fries JF, Bruce B, Cella D. The promise of PROMIS: using item response theory to improve assessment of patient-reported outcomes. Clin Exp Rheumatol 2005;23:S53-7.

Diffusion-Weighted and Diffusion Tensor Imaging in Fibromyalgia Patients: A Prospective Study of Whole Brain Diffusivity, Apparent Diffusion Coefficient, and Fraction Anisotropy in Different Regions of the Brain and Correlation With Symptom Severity[1]

Pia C. Sundgren, MD, PhD, Myria Petrou, MD, Richard E. Harris, PhD, Xiaoying Fan, MD, Bradley Foerster, MD
Neha Mehrotra, Ananda Sen, PhD, Daniel J. Clauw, MD, Robert C. Welsh, PhD

Fibromyalgia (FM) is a chronic pain condition characterized by widespread pain and tenderness that afflicts 2%–4% of the population in industrialized countries (1). It is the second most common rheumatologic disease after osteoarthritis. Although the underlying pathology, mediating the allodynia and hyperalgesia of FM remains poorly understood, a dysfunction in central neurobiologic structures is suspected. In addition to pain, FM patients often present with other syndromes such as irritable bowel syndrome, idiopathic low back pain, and temporomandibular disease syndrome, suggesting a common underlying pathology across these conditions (2).

Although FM is defined by widespread tenderness, experimental data indicate that the enhanced pain sensitivity of FM is not limited to pressure stimuli alone. Individuals with FM also exhibit heightened pain sensitivity in response to multiple other stimuli, including heat, noise, and electricity (3–5). These data, in conjunction with the finding that pain is not localized to a particular body region, suggest that this condition may be largely from the augmented central nervous system processing of pain.

The neurophysiology of pain processing has received increasing interest in recent years and data from different neuroimaging methods such as multiple positron emission tomography (6,7), single photon emission computed tomography (SPECT) (8,9), functional magnetic resonance imaging (10–12), and more recently magnetic resonance (MR) spectroscopy consistently identify the brain structures that are activated during painful conditions in healthy controls (13,14). These structures include the primary and secondary somatosensory cortices, the insula, the anterior cingulate, the thalamus, the dorsal lateral prefrontal cortex, and the basal ganglia (15). Collectively, these regions have been termed the "pain matrix," which is activated in response to painful stimulation. Interestingly, not all of the regions in the pain matrix serve the same functions in encoding pain (16–18). Multiple studies have indicated that pain matrix exhibits abnormal activation patterns in FM, both at baseline and in response to painful stimuli (8–12).

Diffusion-weighted imaging (DWI), which measures the diffusivity of water molecules, is a well-established MR imaging sequence commonly used in clinical practice to detection early ischemia (19). Diffusion tensor imaging (DTI) yields quantitative measures for tissue water mobility as a function of the direction of water motion and is probed by application of diffusion-sensitization gradients in multiple directions (20). Appropriate mathematical

Acad Radiol 2007; 14:839–846

[1] From the Departments of Radiology (P.C.S., M.P., X.F., B.F., N.M., R.C.W.) and Internal Medicine (R.E.H., D.J.C.), and Center for Statistical Consultation and Research (A.S.), University of Michigan, 1500 E Medical Center Drive, Ann Arbor, MI 48109-0030. Received February 28, 2007; accepted March 26, 2007. Supported in part by Department of Army grant DAMD 17/002-0018. **Address correspondence to:** P.C.S. e-mail: sundgren@umich.edu

doi:10.1016/j.acra.2007.03.015

combination of the directional diffusion-weighted images provides quantitative measures of water diffusion for each voxel via the apparent diffusion coefficient (ADC), as well as the degree of diffusion directionality, or anisotropy (21). DTI allows in vivo mapping of the anatomic connections in the human brain; previous studies have identified and confirmed the existence of an anatomic circuitry for the functionally characterized top-down influences on pain processing via brainstem structures in humans (22,23).

Fractional anisotropy (FA) is a measure of the portion of the diffusion tensor from anisotropy.

The aim of the present study was to investigate whether DWI and DTI can depict cerebral abnormalities in fibromyalgia patients and if significant differences in measured ADC histograms between these patients and normal controls exist. We hypothesized that if there were differences between fibromyalgia patients and controls in any brain region, that these abnormalities should be most pronounced in individuals with more severe pain, a lower pain threshold, or cognitions that are known to be associated with a poor prognosis in pain patients.

MATERIALS AND METHODS

The study consists of 19 fibromyalgia patients (16 female, 3 male, ages 20–57 years, mean age 41.0 years) who met the 1990 American College of Rheumatology criteria for fibromyalgia (24) (group 1) as well as 25 pain-free healthy controls (19 female, 6 male, ages 22–59 years, mean age 43.9 years) (group 2), all older than age 18 years were included in the study. The study was approved by our institutional review board, and informed consent was obtained for all participants in the study. All subjects underwent comprehensive screening, during which diagnosis of FM was confirmed for the patient population and comorbidities for both the patient and control groups were evaluated.

Pregnant and left-handed subjects were excluded from the study. Exclusion criteria also included presence of comorbid conditions capable of causing worsening of physical functional status independent of the diagnosis and any psychiatric disorder involving a history of psychosis, current suicide risk or attempt within last 2 years, or substance abuse within the last 2 years.

Subjects who qualified for inclusion on the study were scheduled for a single-day study protocol. This included obtaining the clinical history, pressure testing, and completion of self-report questionnaires followed by a standard pre and postcontrast-enhanced MRI and additional DTI.

The healthy controls subjects were included as being considered healthy after obtaining clinical history, pressure pain testing, completion of a self-report questionnaires, and had the same MR imaging and DTI performed as the fibromyalgia patients.

Imaging

MR imaging.—The MR examinations were performed on a 1.5 T scanner (GE Medical Systems). The conventional MR image examination included: precontrast- and postcontrast-enhanced axial and sagittal T1-weighted images, axial T2-weighted images with fat saturation, axial fluid attenuated inversion recovery, and diffusion-weighted images (Spin-echo Echo planar imaging, b = 1000 s/mm^2, three directions: slice, frequency, and phase-encode, combined on scanner to produce isotropically weighted diffusion image and T2-weighted image) and postcontrast-enhanced T1-weighted images in the coronal projection. Twenty milliliters of Gd-DTPA (Magnevist, Berlex Laboratories) was intravenously injected before postcontrast enhanced images.

DTI.—DTI was obtained using a single-shot, spin-echo EPI technique with a b value of 1000 s/mm^2 for each of nine diffusion encoding directions, plus one b $\cong$ 0 image set, (9,300/minimum/2 [repetition time/echo time/excitations]), field of view 32 cm, matrix 160 $\times$ 128 pixels, 4-mm slice thickness with no gap). Two standard diffusion indices were derived from the DTI data set: ADC and FA.

Imaging Postprocessing and Analysis

Conventional MR imaging.—The conventional MR images were interpreted by a neuroradiology attending. The MR images were specifically evaluated for brain volume loss (visually graded mild moderate or severe), abnormal signal, abnormal contrast enhancement, abnormal diffusion, presence of hemorrhage or mineralization, and any additional abnormalities.

DWI and whole-brain apparent diffusion coefficient histograms.—Whole-brain histograms, gray matter–only histograms, and white matter–only histograms were calculated for each subject according to a previously described method (25). These histograms were normalized to unit area. The mean ADC, the width (standard deviation) of the ADC distributions, the left to right distribution (skewness), and how extended the histogram

(kurtosis) was were evaluated in each subject. Group averages and standard errors of these metrics were then calculated across subjects. A P value $< .05$ was set for statistical significance using Students t-test.

Histograms by group, FM (group 1) and healthy controls (group 2), were then calculated by averaging the unit-normed histograms across the subjects.

DTI.—ADC and FA maps were calculated offline by the following procedure. Initially, images were preprocessed to remove image-to-image misregistration that arises from directional eddy currents during echo planar readout. Directional DWIs were spatially registered to the $b \cong 0$ image set to remove image shear, compression, and shift by an affine transform (26). Mean diffusivity (ie, ADC) and anisotropy (ie, FA) were calculated. These indices are considered quantitative with normal brain values of ADC $\cong 0.7 \times 10^{-3}$ mm^2/second, and FA is a dimensionless value between 0 (isotropic) to approaching 1 (highly anisotropic environments) (20).

To ensure that the correct areas were measured postcontrast T1-weighted images were also registered to the DTI $b \cong 0$ image set such that all images and quantitative maps were viewable in a common spatial frame of reference. Standardized 50 mm^3 circular regions of interest (ROIs) were placed at the following areas, most of them known to be associated with pain processing: amygdala, periaqueductal gray, insular cortex, orbitofrontal cortex, internal capsule, middle thalamus, corpus callosum, dorsolateral prefrontal cortex, cingulate gyrus cortex, parietal white matter, and frontal white matter (Fig 1a–d). All the ROIs for the DTI analysis were placed in normal-appearing gray and white matter brain parenchyma based on the conventional MR imaging of the brain. Mean ADC and FA in the different regions were compared between the two groups. Processing and analysis software described previously were developed in-house using MATLAB (MathWorks, Natick, MA).

Pain Assessment

Clinical pain.—Clinical pain was assessed immediately before the DWI and DTI scans with a 10 cm visual analog scale. This scale visual analog scale was a 10-cm line anchored by the words "no pain" and "worst possible pain" on the left and right end of the scale, respectively.

Experimental pain.—Pressure pain threshold was assessed before the DWI and DTI scans. Discrete pressure stimuli were applied to the subject's left thumbnail using a stimulation device that eliminates any direct examiner/subject interaction. The thumbnail was chosen because it has been shown to be highly representative for overall pressure sensitivity (27). Pain intensity ratings were recorded on the GBSint questionnaire (28). These values were then used to determine the starting pressure levels for the random presentation paradigm (multiple random staircase). During the random staircase testing, the stimulus pressures were determined interactively: a computer program continuously adjusted the stimulus pressures in the three staircases to produce the same response distribution in each subject (29). The results of the three staircases were used to assess evoked pressure pain sensitivity.

Questionnaires

The Center for Epidemiological Studies Depression Scale questionnaire, a 20-item self-report questionnaire assessing symptoms of depression in nonpsychiatric adults, was administered to the FM subjects (30). The Spielberger's Trait Personality Inventory anxiety questionnaire (31) was also given to the FM patients. Specific cognitive beliefs about pain and control over pain, which have previously been noted to be associated with a worse prognosis in chronic pain patients, were assessed by using the Beliefs about Pain Control Questionnaire (32).

Statistical Analysis

For statistical evaluation of differences in whole-brain histograms, gray matter–only histograms, and white matter–only histograms between the two groups, a P value $< .05$ was set for statistical significance using Students t-test.

For statistical evaluation of differences in ADC and FA values between the two groups, a mixed-model analysis of variance model was used. For either ADC or FA as outcome, factors of group, location, and group-location interaction were used as fixed effects. Additionally, side (right or left) was used as a nested fixed effect within location, because the sides were considered to be entities specific to the location. The locations periaqueductal gray and corpus callosum, for which there was a single measurement (no side distinction), were analyzed separately using two-sample t-test for group differences. To account for the clustering effect in the mixed-model analysis, an unstructured variance-covariance pattern is assumed for the observations on the same subject. Post-hoc comparisons between groups within each location were carried out using Bonferroni adjustment for multiple comparisons. Significance was determined using a cutoff of .05 for the P value.

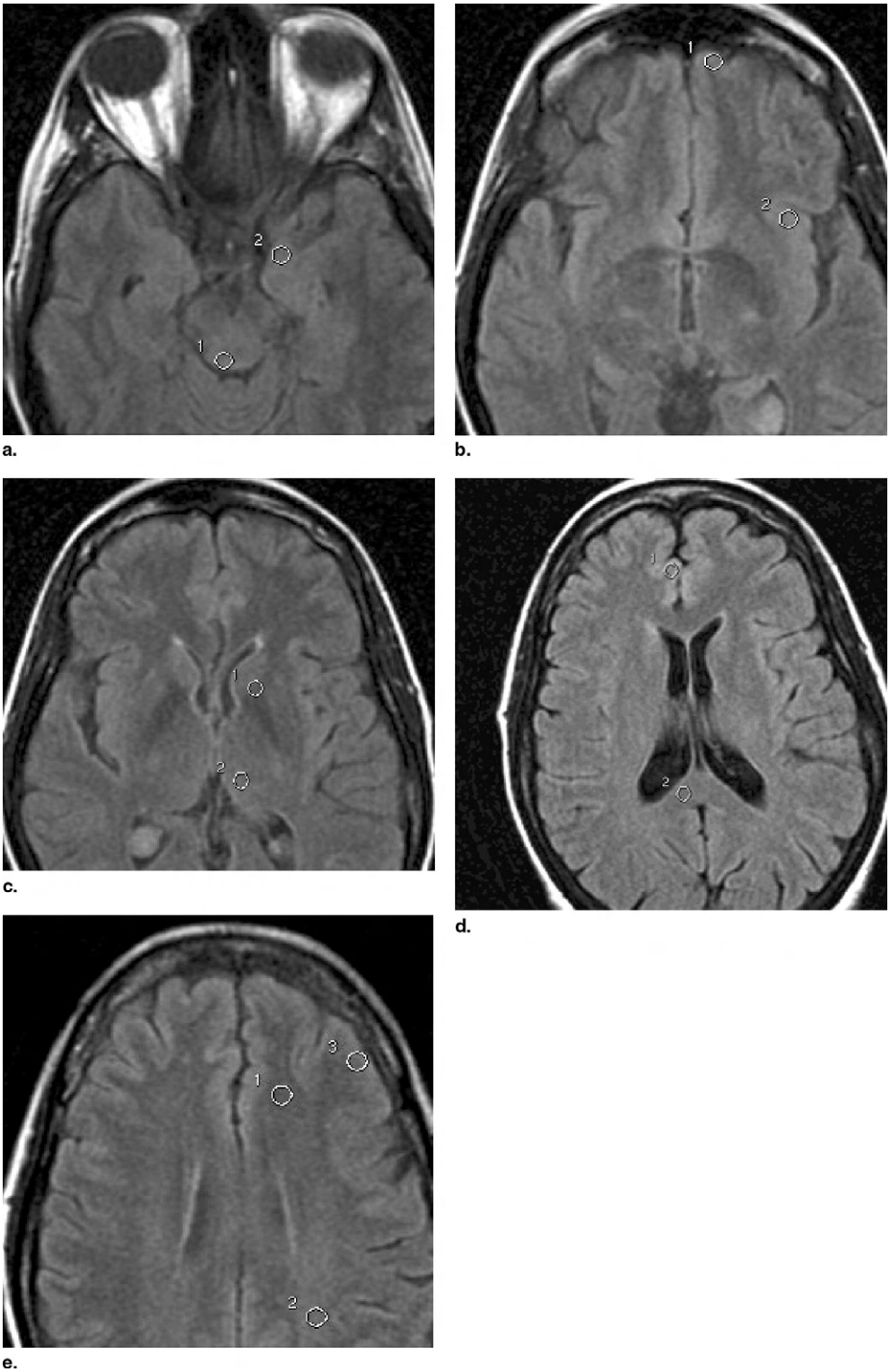


Figure 1. Axial fluid attenuated inversion recovery images showing the different locations of the equal sized regions of interest (ROIs). All ROIs were placed in normal appearing brain parenchyma. The ROI placements for periaqueductal gray (1) and amygdala (2) **(a)**; for orbitofrontal cortex (1), insular cortex (2) **(b)**; internal capsule (1), thalamus (2), **(c)**; for cingulate gyrus cortex (1) and corpus callosum (2) **(d)**; for frontal white matter (1), parietal white matter (2), and dorsolateral prefrontal cortex (3) **(e)**.

To analyze the variability, for each side within each location and each group, the absolute deviations of the observations from their respective means were calculated. These deviations were then analyzed under the framework of a mixed-model analysis of variance as described in the previous paragraph. Because the absolute deviations from the mean roughly estimate a scale multiple of the standard deviation, this approach is deemed as a reasonable one to analyze the variability. Further note that this is a straightforward adaptation of Levene's method (33) of testing homogeneity of variance under the usual analysis of variance framework to the case of correlated observations.

Nonparametric correlations between clinical outcomes and DTI measurements were made in SPSS (SPSS version 14.0 (Chicago, IL).

RESULTS

The conventional MR image was normal with respect to brain parenchyma in all subjects. Incidental finding of a right internal carotid artery aneurysm was noted in one of the normal controls and perimucosal thickening of one or several sinuses were present in a few of the subjects in both groups.

There was no significant difference in whole-brain diffusivity between the two groups. Nor was there any significant difference between the segmented gray or white matter–only diffusivity between the groups.

As expected, both the average ADC and FA values, with P value $< .0001$ for each outcome, were significant effect by brain location (ie, depended on where in the brain the measures had been performed). However, this did not differ between the two *groups* ($P = .7114$ and .9808 for ADC and FA, respectively) or sides ($P = .2713$ and .4208 for ADC and FA, respectively). Group-location interaction was statistically significant for FA ($P = .0005$), but not for ADC ($P = .3781$). This meant that with respect to FA, the group differences, although not significant overall, exhibited differential patterns across different locations.

The FA values were significantly lower in the right thalamus in the FM patients compared with those obtained in healthy controls (mean [SD] FM: 0.258 (0.022); HC: 0.278 (0.035); $P = .02$) (Table 1). None of the other locations exhibited any significant group differences.

Neither the main effects of brain location, group, nor the group-location interaction were found to have a statistically significant effect on variability in ADC ($P = .3723$, .1922, and .9005, respectively). The effect of side, on the other hand, was statistically significant ($P = .0103$) for ADC variability. Because side is a nested factor within location, it is meaningful to consider the differences between sides only within each specific location. However, none of those differences were statistically significant. With respect to the variability in FA, there was a statistically significant difference across brain locations ($P < .0001$). All other factors were deemed nonsignificant.

Table 1
ADC (Mean and SD) and FA (Mean, SD) and *P* Value in Right Thalamus in the Two Groups

	FM Patients (19)	HC (25)	*P* Value
ADC (mean [SD]) × 10^{-6} mm	7.14 (0.30)	7.20 (0.28)	NS
FA (mean [SD])	0.258 (0.022)	0.278 (0.035)	.02

ADC: apparent diffusion coefficient; FA: fraction anisotropy; SD: standard deviation.

Because the right thalamus was the region that was statistically different between patients and controls, we examined the within-group relationship between the severity of FM symptoms and findings and this measure. A negative correlation was seen between the FA values in the right thalamus and clinical pain ($r = -0.50$, $P = .049$) in the FM group, indicating that those individuals with worse clinical pain had a lower value. We also noted a negative correlation was seen between the FA values in right thalamus and the belief in "external" pain control ($r = -0.72$, $P = .005$) in the FM group, indicating that these low right-thalamic FA values were also significantly associated with a cognition known to be negatively associated with prognosis in chronic pain. Although no other values were statistically significant, lower right-thalamic FA values within the FM group were associated with greater numbers of tender points, higher levels of depressive symptoms, and a low pressure pain threshold (Table 2).

DISCUSSION

Previous neuroimaging studies, such as functional magnetic resonance imaging and MR spectroscopy, and smaller numbers of studies using DTI have identified and confirmed the existence of an anatomical circuitry for the functionally characterized top-down influences on pain

Table 2
Correlation of Clinical Outcomes With FA Values in Right Thalamus

Clinical Outcome	R (correlation)	*P* Value
Tender point	−0.47	NS
VAS—clinical pain	−0.50	<.05
Depression	−0.23	NS
Anxiety	−0.07	NS
BPCQ—powerful doctor	−0.72	<.005
BPCQ—chance	0.36	NS
BPCQ—internal	0.07	NS
Pressure pain testing—low	0.12	NS
Pressure pain testing—medium	0.14	NS
Pressure pain testing—high	0.16	NS

FA: fraction anisotropy; VAS: visual analog scale; BPCQ: Beliefs about Pain Control Questionnaire.

processing via brainstem structures in humans (10,11,14,15,22,23). Several studies have suggested that the widespread pain sensitivity in FM is caused by a central nervous system–based pain processing problem (3–5,34,35). Multiple functional neuroimaging modalities have now been used to identify differences in regional blood flow or neuronal activity in pain processing regions between FM patients and controls (6–12,36). However, to our knowledge, no previous studies have used DTI to assess ADC, whole-brain histograms, or FA in FM.

Our primary findings are that there were differences in FA between FM patients and controls, and that this was most pronounced in the right thalamic region. Within the FM group, the magnitude of these differences were statistically greater in those individuals with worse clinical pain and an external locus of pain control, and nonsignificantly associated with other clinical parameters of disease severity, suggesting that these findings are clinically relevant rather than spurious findings.

These findings are in agreement with previous SPECT studies (8,9) suggesting that thalami together with other focal brain structures play an important role in the pain modulation and processing in this condition. A few previous SPECT study of FM patients revealed diminished baseline cerebral blood flow (rCBF) in bilateral thalami and caudate nuclei in FM patients compared with healthy controls (8,9). Similar findings with reduced baseline cerebral blood flow in the inferior dorsal pons, right lentiform nucleus, and the right thalamus with a similar trend in the left thalamus in FM patients compared with healthy controls have been recently been demonstrated in a MRI perfusion study (36).

It is known that the lateral structures including the ventral lateral thalamic nuclei are thought to encode pain intensity, whereas the medial structures including the dorsal medial thalamus are thought to process unpleasant or affective aspects of pain (15–18). In the present study, the placement of the ROI was more in the middle of thalamus and therefore the findings might be influenced from both lateral and medial aspect of the nuclei. Therefore future investigation should focus on evaluation of the FA and ADC in thalami more specific to the ventrolateral thalamic nuclei and to the dorsomedial thalamic nuclei. By looking at more well-defined areas in the thalami, more distinct differences between FM patients and controls might be discovered. Also functional MRI analysis of other defined regions such as anterior and dorsal aspects of insula and cingulate gyrus might increase the insight in underlying pathology and pain sensitivity in fibromyalgia.

However, because we are unable to demonstrate any significant differences in FA or ADC values between the two groups in other brain regions, it is possible that diffusion-weighted or diffusion tensor imaging might be a less sensitive method to identify differences between patients and controls, compared with other MR imaging methods such as functional magnetic resonance imaging or MR spectroscopy. An alternative explanation for the lack of differences between the two groups in the present study is that there are no significant alterations in diffusivity of water in the brain and no detectable changes in FA or ADC in FM patients. However, it cannot be excluded that the size of the ROI in the present study was too large and that more specific target areas such as medial and lateral aspect of thalamus, and anterior or posterior insula regions have to be evaluated with smaller sized ROI if any differences using DWI/DTI are to be detected.

As with any other abnormalities detected in functional imaging, the precise cause for these abnormalities is unclear. Because of the focal nature of these findings, and other accumulating evidence regarding fibromyalgia, it is not likely that the abnormalities identified in this study are due to an ongoing demyelization or even axonal injury, but instead are more likely the result of neuronal dysfunction. It can be speculated that if the tissue is less organized or the axons dysfunctional, it might be seen as a reduction in the main directionality combined with alterations in the other diffusion directions resulting in a more round and less spheric/ellipsoid appearance of the diffusion directionality as can be seen in a more isotropic environment. This idea can be supported by the normal

ADC values found here in the same region. The diffusivity as measured by ADC and the anisotropy as measured by FA represent just a part of the information available from the diffusion tensor. Examination of individual eigen values, which reflect the diffusivities in longitudinal or transverse directions with respect to fiber tracts, may add additional information and tissue characterization and can be applied in future investigations.

Our study has limitations. Although the number of subjects included in the study is comparable or larger than other studies looking into FM with functional neuroimaging techniques, it may still be a small number of subjects when looking for subtle differences between groups. A small sample size can be especially limiting when one considers the heterogeneity in clinical presentation of the patient group, as well as the comorbidities that can are often associated with FM. Another limitation is that we have not performed specific brain volume segmentation for brain volume loss, but none of the 19 fibromyalgia patients had any notable brain atrophy, and their conventional brain MR images did not demonstrate any morphologic or structural brain abnormalities.

In conclusion, our study provide evidence from another functional imaging modality that there are subtle abnormalities in neuronal function in pain processing regions of the brain in fibromyalgia. In particular, these data support previous data indicating that thalami play a significant role in the pain processing in FM. Future investigations could focus on differences in different parts of the thalamic nuclei, or on more specific regions of interest in other areas such as the insula, which might yield more information and insight to the pathogenesis of this disease.

ACKNOWLEDGMENTS

We acknowledge the support of Laura Mayo-Bond, clinical subjects coordinator study coordinator and data collector for this study, and Suzan Rohrer, BA, RT(B), (MR), Department of Radiology, for her dedication to the participance of this study and for performing the MR examinations in timely and efficient manor.

REFERENCES

1. Wolfe F, Ross K, Anderson J, et al. The prevalence and characteristics of fibromyalgia in the general population. Arthr Rheum 1995; 38:19–28.
2. Clauw DJ, Chrousos GP. Chronic pain and fatigue syndromes: overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. Neuroimmunomodulation 1997; 4:134–153.
3. Petzke F, Clauw DJ, Ambrose K, et al. Increased pain sensitivity in fibromyalgia: effects of stimulus type and mode of presentation. Pain 2003; 105:403–413.
4. Arroyo JF, Cohen ML. Abnormal responses to electrocutaneous stimulation in fibromyalgia. J Rheumatol 1993; 20:1925–1931.
5. Lorenz J Hyperalgesia or hypervigilance? An evoked potential approach to the study of fibromyalgia syndrome. Zeitschr Rheumatol 1998; 57(Suppl 2):19–22.
6. Aziz Q, Thompson DG, Ng VW, et al. Cortical processing of human somatic and visceral sensation. J Neurosci 2000; 20:2657–2663.
7. Jones AK, Brown WD, Friston KJ, et al. Cortical and subcortical localization of response to pain in man using positron emission tomography. Proc R Soc Lond B Biol Sci 1991; 244:39–44.
8. Mountz JM, Bradley LA, Modell JG, et al. Fibromyalgia in women. Abnormalities of regional cerebral blood flow in the thalamus and the caudate nucleus are associated with low pain threshold levels. Arthr Rheum 1995;38:926–938.
9. Kwiatek R, Barnden L, Tedman R, et al. Regional cerebral blood flow in fibromyalgia: single-photon-emission computed tomography evidence of reduction in the pontine tegmentum and thalami. Arthr Rheum 2000; 43:2823–2833.
10. Gracely RH, Petzke F, Wolf JM, et al. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthr Rheum 2002; 46:1333–1343.
11. Giesecke T, Gracely RH, Grant MA, et al. Evidence of augmented central pain processing in idiopathic chronic low back pain. Arthr Rheum 2004; 50:613–623.
12. Cook DB, Lange G, Ciccone DS, et al. Functional imaging of pain in patients with primary fibromyalgia. J Rheumatol 2004; 31:364–378.
13. Ross AJ, Sachdev PS. Magnetic resonance spectroscopy in cognitive research. Brain Res Brain Res Rev 2004; 44:83–102.
14. Grachev ID, Fredrickson BE, Apkarian AV. Abnormal brain chemistry in chronic back pain: an in vivo proton magnetic resonance spectroscopy study. Pain 2000; 89:7–18.
15. Brooks J, Tracey I. From nociception to pain perception: imaging the spinal and supraspinal pathways. J Anat 2005; 207:19–33.
16. Singer T, Seymour B, O'Doherty J, et al. Empathy for pain involves the affective but not sensory components of pain. Science 2044; 303:1157–1162.
17. Critchley HD, Wiens S, Rotshtein P, et al. Neural systems supporting interoceptive awareness. Nat Neurosci 2004; 7:189–195.
18. Craig AD, Chen K, Bandy D, et al. Thermosensory activation of insular cortex. Nat Neurosci 2000; 3:184–190.
19. Mosely M, Cohen Y, Kucharczyk J, et al. Diffusion-weighted MR-imaging of anisotropic water diffusion in cat central nervous system. Radiology 1990; 176:439–445.
20. Basser PJ, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J Magn Reson 1996; Series B 111:209–219.
21. Sundgren PC, Dong Q, Gomez-Hassan D, et al. Diffusion tensor imaging of the brain. Review of clinical applications. Neuroradiology 2004; 46:339–350.
22. Hadjipavlou G, Dunckley P, Behrens TE, et al. Determining anatomical connectivities between cortical and brainstem pain processing regions in humans: a diffusion tensor imaging study in healthy controls. J Pain 2006; 123:169–178.
23. Seghier ML, Lazeyras F, Vuilleumier P, et al. Functional magnetic resonance imaging and diffusion tensor imaging in a case of central post-stroke pain. J Pain 2005; 6:208–212.
24. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter criteria committee. Arthritis Rheum 1990; 33:160–172.
25. Welsh RC, Rahbar H, Foerster B, et al. Brain diffusivity in patients with neuropsychiatric systemic lupus erythematosus with new acute neurological symptoms. J Magn Reson 2007. In press.
26. Meyer CR, Boes JL, Kim B, et al. Demonstration of accuracy and clinical versatility of mutual information for automatic multimodality image fusion using affine and thin plate spline warped geometric deformations. Med Image Anal 1997; 1:195–206.

27. Petzke F, Khine A, Williams D, et al. Dolorimetry performed at 3 paired tender points highly predicts overall tenderness. J Rheumatol 2001; 28:2568–2569.
28. Petzke F, Harris RE, Williams DA, et al. Differences in unpleasantness induced by experimental pressure between patients with fibromyalgia and controls. Eur J Pain 2005; 9:325–335.
29. Gracely RH, Lota L, Walter DJ, et al. A multiple random staircase method of psychophysical pain assessment. Pain 1988; 32:55–63.
30. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Measur 1977; 1:385–401
31. Spielberger CD, Gorsuch RC, Lushene RE, et al. (1983). Manual for the State Trait Anxiety Inventory (Form Y): ("Self-evaluation questionnaire"). Palo Alto, Ca: Consulting Psychologists, 1983.
32. Skevington SM. A standardized scale to measure beliefs about controlling pain (BPCQ): a preliminary study. Psychol Health 1990; 4:221–232.
33. Levene H. (1960). In: Olkin I et al, eds. Contributions to probability and statistics: essays in honor of Harold Hotelling. Stanford, Ct: Stanford University Press, 1960; 278–292.
34. Petrou M, Foerster B, Fan X, et al. Two D-CSI MR spectroscopy in the evaluation of fibromyalgia patients: a prospective study comparing fibromyalgia patients with normal healthy controls. European Society of Neuroradiology Annual Meeting, 2005;78.
35. Petrou M, Foerster B, Fan X, et al. Metabolite abnormalities in potential pain processing brain regions of fibromyalgia patients using MR spectroscopy. European Congress of Radiology 2006; 313.
36. Foerster BR, Petrou M, Clauw DJ, et al. Cerebral perfusion differences in pain processing regions of fibromyalgia patients using MR perfusion techniques [abstract]. To be presented at the European Congress of Radiology 2007, Vienna, Austria.

The Journal of Pain, Vol 8, No 4 (April), 2007: pp 343-348
Available online at www.sciencedirect.com

ELSEVIER

Assessor Status Influences Pain Recall

David A. Williams,* Karen M. Park,† Kirsten R. Ambrose,* and Daniel J. Clauw*

*Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan; and
†Michigan Pain Specialists, PLLC, Ann Arbor, Michigan.

Abstract: **Anecdotal clinical reports suggest that patients report differing levels of pain, depending on the status within the medical hierarchy of the individual gathering the pain rating. This observation has clinical relevance, given the practice of delegating the assessment of pain to lower status clinic staff members. In this study, both pain and mood were assessed in 70 patients diagnosed with low back pain at pretreatment, immediately after epidural lumbar injection, and again 2 weeks later by phone. At the 2-week follow-up, patients were also asked to recall the postprocedural rating that they had given immediately after the injection. This rating was obtained by either the treating physician or by a research assistant who was present at the time of injection, on a randomly determined basis. Current ratings of pain and mood did not differ for either group before the epidural injection, after the epidural injection, or at the 2-week follow-up. Two-week recall of postprocedural pain did, however, differ depending on assessor status. Those called by the physician provided recalled pain ratings that closely matched the ratings provided immediately after the procedure. Those called by the research assistant provided ratings that were 86% higher (that is, worse) than their original ratings. This status-driven bias in recalled postprocedural pain reporting is discussed in the context of social demands inherent in the physician-patient relationship, with implications for assessing treatment effectiveness in clinical practice and research.**

Perspective: ***Accurate assessment of patients' pain is critical to effective pain management and treatment planning. This study found evidence of a status-based bias in which physicians elicited lower ratings of previously experienced pain associated with treatment procedures than did staff members of lower status.***

Key words: *Demand characteristics, pain, assessment, recall bias, pain report.*

Patients in medical settings receive pain assessments more frequently today than at any other time in history. Mandates from the Joint Commission for Accreditation of Healthcare Organizations[9] and from the campaign to promote pain as the 5th vital sign[29] highlight efforts to bring increased awareness to the importance of pain and its management in medical settings. Effective clinical responses to pain depend heavily on timely assessment and on the quality of patients' pain reports. Given there are no direct biomarkers of pain, subjective patient reports of pain are the best alternative. These ratings, however, are influenced by a number of factors termed "reporting biases." The many reporting biases affecting pain assessment have been reviewed elsewhere but include such factors as motivation, selective memory, mood influences on pain processing and recall, personality, current, recent and peak pain intensity influences on recalled pain, influences of ingested substances, cognitive ability and capacity to summarize subjective experiences into a single numeric value, and ambiguities of recalling pain over time.[1,3-6,8,10,22,24-27] Whether these factors are indeed biases as the term implies (that is, suggesting inaccuracy) or integral facets of the experience of pain is debatable.

Most studies of reporting biases have focused on patient-centered influences (for example, memory, mood, and so forth); however, a few studies have focused on environmental (for example, interpersonal) factors. For example, ratings of experimental pain tolerance have been observed to be higher when the assessor was of the

Received April 3, 2006; Revised September 15, 2006; Accepted October 14, 2006.

Supported in part by Department of Army grant DAMD17-00-2-0018.

This research was conducted at the Georgetown University Medical Center.

Address reprint requests to David A. Williams, PhD, University of Michigan, Chronic Pain and Fatigue Research Center, 24 Frank Lloyd Wright Drive, PO Box 385, Lobby M, Ann Arbor, MI 48106. E-mail: daveawms@umich.edu

1526-5900/$32.00

doi:10.1016/j.jpain.2006.10.005

opposite sex.[11] A second study showed similar findings for male patients assessed by a female patient; but, unlike the first study, female patients assessed by male patients tended to report greater pain.[12] At least 1 study has found no differences as the result of sex.[19]

Credibility and status within the medical hierarchy is another interpersonal factor known to affect clinical outcomes across diverse clinical populations. For example, appearances and attire (such as, white coats) can be used as a means of substantiating impressions of professionalism and trust in clinical settings.[13,15,16,23] Once trust is established, issues of status tend to be minimized, as has been shown in several studies finding equivalence in satisfaction between health care offered by physicians and nurse practitioners.[2,7,17] For briefer encounters, however, status appears to retain its importance, as in the assessment of pain. For example, several clinical reports have demonstrated that physicians were more likely to elicit lower pain ratings from patients compared with pain ratings obtained by research assistants or disinterested third parties asking about the same pain condition over the same time period.[14,18] Explanations for this effect have included (1) wanting to please the doctor, (2) not wanting to be a burden to the doctor, and (3) not wanting to be rejected by the medical staff for being a problem patient.

These clinical reports are intriguing and suggest the need for a more rigorous controlled investigation of the extent to which clinical pain reports are influenced by pain assessor status.[11] The current study is a randomized study of recalled clinical pain where assessor status (ie, physician or research assistant) was randomly manipulated between 2 groups of patients having the same treatment (ie, nerve block) for the same pain condition (low back pain). Irrespective of pain reports provided at the time of the block, we hypothesized that at 2-week follow-up, patients would recall their pain as being higher after the nerve block if assessed by a research assistant than if assessed by the physician who had performed the block.

Materials and Methods

Participants

Participants were 70 consecutive referrals meeting inclusion criteria to an anesthesia pain clinic located at Georgetown University Hospital in Washington, DC. All participants completed an informed consent process approved by the university's institutional review board. To be included in the study, the investigators screened participants who presented to the pain clinic with a diagnosis of low back pain (ICD9 code = 724.2) and were currently scheduled to receive a lumbar epidural injection for the management of low back pain. This sample was composed of 41 women and 29 men. The mean age of the sample was 52.7 (SD = 16.1) years. The sample included white (67%) and black (23%) individuals. The educational level of the sample included 50% who had completed at least 1 college degree and an additional 44% who had completed high school. Twenty percent of the sample was involved in legal action or disability associated with their back injury.

Procedures

Before receiving the nerve block, all participants completed a brief (pretreatment) self-report battery of questionnaires that included measures of current pain intensity, expected pain relief, and ratings of mood (depressed affect, anxiety, anger). These questionnaires were administered by the same female research assistant for each participant.

All participants received an injection containing lidocaine to infiltrate the skin and an epidural corticosteroid (Depo-Medrol; Pfizer, New York, NY) for pain relief. Within 30 minutes of receiving the block, all participants were asked by the research assistant (female), in the presence of the treating physician (female), to provide a pain rating and to again rate depressive, anxious, and angry mood (post-treatment assessment). Thus, this post-treatment pain rating was collected while holding sex constant and having both low- and high-status individuals present. In addition, both the physician and the research assistant wore standard white lab coats during this face-to-face assessment to minimize biases toward appearance.

Two weeks later, all participants were contacted by phone and asked to provide a rating of their current pain and mood (follow-up assessment) as well as to recall the amount of pain that they had experienced immediately after the nerve block (recall of the post-treatment rating).

In this study, all participants had the same diagnosis and were treated identically with the exception that the assessor for the 2-week follow-up phone call was determined randomly just before making the call. The call was made by either the physician who had performed the nerve block (high status) or the research assistant who had been present at the time of the nerve block (low status). In either case, the call was made by someone whom the participant had met in person at the time of the initial nerve block 2 weeks earlier. In making the follow-up phone call, both the treating physician and research assistant followed the same scripted phone interview. The same female research assistant was present for all participants, and 93% of the cases were seen by the same female physician. Five cases were seen by a second female physician of equal medical status.

Outcomes

Pain

For each assessment of pain (current, expected, recalled), participants completed a standard 11-point numeric rating scale (NRS) that ranged from "0, no pain" to "10, most severe pain imaginable." This type of pain rating scale is commonly used in clinical practice and is considered to be a clinically expedient and valid method of assessing pain.[20]

Affect

Affect was assessed with the use of the Profile of Mood States Linear Analogue Scales (POMS-LASA).[28] Like the pain NRS, the POMS-LASA uses an 11-point NRS to assess 3 current mood states: depressed affect, anxiety, and anger.

Randomization

Random-number tables were used to assign either the physician or the research assistant to conduct the follow-up assessment of a given participant. Using this method, the treating physician was assigned to 38 participants and the research assistant was assigned to 32 participants.

Analytic Methods

Primary Analysis

To determine whether deviations in recalled post-treatment pain ratings and the original post-treatment pain ratings were influenced by assessor status, an analysis of covariance (ANCOVA) was used. The ANCOVA used the originally reported post-treatment pain rating as a covariate, thus identifying deviations in the recalled rating across time and between the 2 groups.

Secondary Analyses

In addition to the status of the assessor, recalled pain intensity is potentially influenced by a number of factors including (1) demographics (for example, age and sex); (2) pain intensity before the block, pain intensity after the block, and pain intensity at the time of recall; and (3) affect (depressive symptoms, anxiety, and anger) at each of the assessment intervals. Secondary analyses occurred in 2 steps. In step 1, recalled pain intensity was correlated with each of the potentially influential variables listed above. In step 2, each of the variables involved in a statistically significant association with recalled pain intensity was entered into a regression model. Backwards regression modeling was then used to identify the most salient variables involved in the prediction of recalled pain intensity. Backwards regression is an atheoretical, empirically driven statistical technique for explaining the variance in a given dependent variable when the most parsimonious set of variables (ie, from a larger initial field) is desired. Modeling terminated when only statistically significant variables remained, thus rendering both a salient and parsimonious prediction model.

Identical correlational and regression modeling procedures were used to identify the most salient clinical variables associated with the magnitude of the discrepancy between the postprocedural pain rating and the 2-week recall of that value.

Results

Equivalence Between Groups

Nonparametric tests and *t* tests were used to identify any differences in the 2 groups with regard to pretreatment baseline, post-treatment, or follow-up characteristics, such as: (1) demographics (for example, age, sex, education, cultural background, and compensation/litigation status), (2) pain intensity, (3) pain relief immediately after the block, and (4) affect (depressive symptoms, anxiety, and anger) (Table 1). There were no statistically significant differences between the groups on any of these measures, lending confidence to the success of the randomization process and the equivalence of the groups.

Table 1. Equivalence Measures Between Groups

	Status of Person Assessing Recalled Pain			
Baseline Variables	Physician		Research Assistant	
Demographics				
Age (mean)	55.5 (SD = 17.0)		49.4 (SD = 14.6)	
Sex (frequency)	F = 19 M = 19		F = 22 M = 10	
Education	50% College		50% College	
Cultural background	68% White		65% White	
Litigation/compensation	7 Cases		7 Cases	
Current pain	*Mean*	*SD*	*Mean*	*SD*
Preblock	5.1	2.2	5.4	2.6
Postblock	2.9	2.3	2.8	2.2
Two-week follow-up	4.7	2.9	4.5	2.6
Recalled pain				
Two-week follow-up	3.2*	2.5	5.2*	2.4
Mood ratings	*Mean*	*SD*	*Mean*	*SD*
Preblock				
Depression	1.9	2.2	2.4	2.9
Anxiety	3.9	3.0	4.8	3.3
Anger	1.9	3.0	1.9	2.7
Postblock				
Depression	0.95	1.8	1.5	2.5
Anxiety	1.6	2.4	2.2	2.7
Anger	0.8	2.1	0.9	2.1
Two-week follow-up				
Depression	1.2	1.7	2.1	2.7
Anxiety	2.8	2.6	3.2	2.8
Anger	1.2	2.3	1.5	2.6

*$P < .05$.

Primary Analyses

The amount of pain reported at post-treatment did not differ significantly by group. As a sample, the mean drop in pain intensity between baseline and post-treatment was 41% (SD = 0.57). Two weeks later, patients in both groups were reporting current pain intensity levels consistent with their preblock values, which also did not differ between groups (Table 1). Taking into account the original post-treatment rating, ANCOVA revealed a significant difference between groups in recalled pain, based solely on the status of the individual performing the follow-up pain assessment ($F[1, 67] = 14.86$, $P < .0001$). Patients being assessed by the physician at follow-up recalled their post-treatment pain level such that on average, there was only a 10% deviation between the

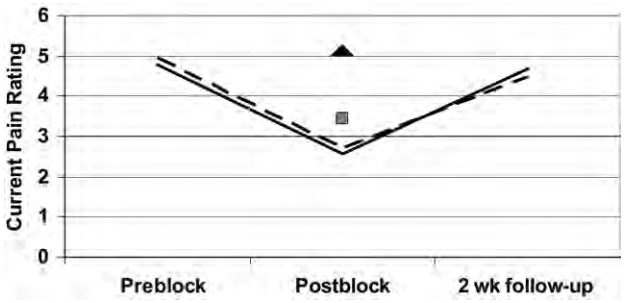


Figure 1. Recalled pain intensity ratings superimposed on current pain ratings at 3 time points (pretreatment, post-treatment, and 2-week follow-up). Current pain ratings: ——, the group called by the physician (n = 38); – – –, the group called by the research assistant (n = 32). Mean recalled postblock pain ratings: ▩, the group called by the physician (n = 38); ▲, the group called by the research assistant (n = 32).

original post-treatment rating and the follow-up recall rating. Patients being assessed by the research assistant at follow-up, however, revealed 86% inflation over the original rating when making the same comparison (Fig 1). Post hoc evaluations revealed equivalent findings for both physicians.

Secondary Analyses

Correlational analyses were performed to better identify the many factors that might be meaningfully associated with recalled pain intensity. Of the various demographic, pain, and mood measures listed in the methods section, only 9 variables showed statistically significant relations with recalled pain at post-treatment: age and sex; pretreatment pain intensity, depression, expected pain relief; postprocedural pain intensity, depression and anger; and assessor status (Table 2).

To better refine an understanding of the most salient predictors of recalled pain intensity, all variables involved in significant associations with recalled pain were entered into a backwards regression model. A high degree of shared variance between the predictor variables resulted in a final parsimonious model involving only 3 variables and accounting for 38% of the variance in recalled pain intensity: age, original postprocedural pain rating, and assessor status (Table 3). Fourteen percent of the variance in recalled pain after the nerve block was due to age, with younger patients recalling higher values than older patients. The original post-treatment rating accounted for 12% of the variance in the recalled ratings and the status of the assessor accounted for an additional and unique 11% after all other sources of variance were considered.

Table 2. Factors Correlating Significantly With Recalled Pain Intensity

Variables	*R*
Age (y)	−0.37
Sex (women having greater pain)	0.29
Preblock pain intensity	0.36
Preblock depression	0.30
Expected postblock pain intensity	0.30
Immediate postblock pain intensity	0.40
Postblock depression	0.32
Postblock anger	0.27
Follow-up assessor status	0.37

All correlations shown have significant *P* values of at least $P < .05$.

For age, sex, and assessor status, point biserial correlation coefficients are reported.

Table 3. Predictors of 2-Week Recalled Postprocedural Pain Intensity

R^2	*F (3,66)*	*Variable*	*T*	*P*
0.38	12.76			< .0001
		Age	2.4	< .02
		Postprocedural rating	3.8	< .001
		Assessor status	3.4	< .001

R^2 indicates percent variance accounted for by the statistical model.

F-statistic and associated *P* value indicates statistical significance of the model.

T-statistic and associated *P* values indicate the statistically significant contribution to the model.

Identical analytic procedures sought to identify the variables most predictive of the magnitude of the discrepancy between the original postprocedural pain rating and the 2-week recalled pain rating. The only significant correlation was with assessor status ($r_{pb} = 0.40$, $P < .001$), suggesting greater discrepancies with lower status.

Discussion

Lumbar epidural injections led to a temporary 41% reduction in pain for both groups in this study. Two weeks later, when patients were asked to recall the amount of pain experienced after the nerve block, the recalled pain intensity differed significantly, depending on whether the pain assessor was the treating physician or the research assistant. Recalled pain ratings provided to the treating physician tended to be lower and more closely matched the post-treatment pain rating obtained at the time of the nerve block. The research assistant, on the other hand, was more likely to be given a rating that was considerably higher than the original rating and that more closely matched the pretreatment pain rating.

Such a finding is particularly important, given the guidelines for frequent assessment of pain and the tendency to delegate this responsibility to a variety of medical staff members. Given that the goal of more frequent pain assessment is to better guide the management of pain, it appears that not only the instrument but also the assessor may need to be standardized to improve the reliability of pain reporting over time. An advantage of the current study design was that all factors were controlled and held constant between the 2 groups up until the follow-up phone call was made. Thus, all participants were treated identically except for the status of the individual making the phone call. This design lends confi-

dence in interpreting the observed discrepancy as being due to status.

There is a possible alternative explanation to the results of this study regarding the timing of the bias. As we interpreted the findings, the bias occurred at the follow-up assessment, with physicians obtaining lower recalled ratings than the research assistant. Alternatively, the bias could have occurred for all patients at the posttreatment assessment, given that the physician was present at that rating as well. The presence of the high-status physician might have outweighed any influence of the lower-status research assistant, resulting in all patients biasing their ratings lower in the presence of the physician. At the time of recall, the physician obtained pain reports for half of the participants, who indicated only a small change from their original pain report. The other half of the participants gave recalled pain reports to the research assistant and may have felt more comfortable providing a higher pain rating in the absence of the physician. Although questions regarding the timing of the bias are unanswered by this study, either interpretation of these data implies that assessor status influences pain reporting and underscores the need for consistency in the use of pain assessors over time.

Resembling at least 1 other study of similar design,[21] this study did not provide support for the influence of other suspected biasing factors on pain recall such as current pain intensity and affect at the time of the block and at the time of recall. Similarly, other environmental factors such as attractiveness and appearance of the assessors were controlled by the design. Support was obtained for age and the original postprocedural pain report to play important roles in determining recalled pain intensity. Interestingly, the status of the assessor accounted for just as much of the variance in recall as did the original postprocedural pain rating.

Several potential limitations should be considered when reviewing this study. Although the current design provided confidence that any effect was due to assessor status by using a single randomized experimental manipulation (physician versus research assistant making the follow-up call), findings from tightly controlled experiments of this nature may not generalize well into clinical practice. For example, it is unlikely that both high- and low-status personnel will be always present at the time a given pain rating is obtained. Future studies may want to extend these findings by using designs that counterbalance status before and after medical procedures. Another potential limitation is that while scripted, the phone-based assessments were not audiotaped; thus, the ability to conduct post hoc qualitative analyses of participants' responses to each assessor's inquiries was not possible.

The clinical and research implications surrounding this type of recall bias are several. Given that much of clinical practice involves asking patients to recall pain over a time period, it is important to recognize the possibility that a physician (being of high status) might be given a lower rating than a staff member of lower status. From these data, it cannot be concluded that physicians or research assistants yield more or less accurate ratings—only that the intensity ratings significantly differ between the 2 statuses. Procedurally, this suggests that serial pain assessments might best be conducted by individuals of similar status over time. This recommendation would be the same for research as for clinical applications.

Acknowledgments

The researchers would like to acknowledge Ann T. Thomas, MA, for her contributions to this project.

References

1. Broderick JE, Stone AA, Calvanese P, Schwartz JE, Turk DC: Recalled pain ratings: A complex and poorly defined task. J Pain 7:142-149, 2006

2. Brown SA, Grimes DE: A meta-analysis of nurse practitioners and nurse midwives in primary care. Nurs Res 44:332-339, 1995

3. Eich E: On the accuracy of memory for pain. APS J 2:192-194, 1993

4. Eich E, Reeves JL, Jaeger B, Graff-Radford SB: Memory for pain: Relation between past and present pain intensity. Pain 23:375-380, 1985

5. Gedney JJ, Logan H: Pain related recall predicts future pain report. Pain 121:69-76, 2006

6. Gendreau RM, Hufford MR, Stone AA: Measuring clinical pain in chronic widespread pain: Selected methodological issues. Best Pract Res Clin Rheumatol 17:575-592, 2003

7. Horrocks S, Anderson E, Salisbury C: Systematic review of whether nurse practitioners working in primary care can provide equivalent care to doctors. BMJ 324:819-823, 2002

8. Jamison RN, Sbrocco T, Parris WC: The influence of physical and psychosocial factors on accuracy of memory for pain in chronic pain patients. Pain 37:289-294, 1989

9. JCAHO: Joint Commission on Accreditation of Health Care Organizations: Background on the development of the Joint Commission standards on pain management. 2003

10. Kahneman D, Frederickson B, Schreiber C, Redelmeier DA: When more pain is preferred to less: Adding a better end. Psychol Sci 4:401-405, 1993

11. Kállai I, Barke A, Voss U: The effects of experimenter characteristics on pain reports in women and men. Pain 112: 142-147, 2004

12. Levine FM, DeSimon LL: The effects of experimenter gender on pain report in male and female subjects. Pain 44:69-72, 1991

13. Lill MM, Wilkinson TJ: Judging a book by its cover: Descriptive survey of patients' preferences for doctors' appearance and mode of address. BMJ 331:1524-1527, 2005

14. Long DM, Erickson DE: Stimulation of the posterior columns of the spinal cord for relief of intractable pain. Surg Neurol 4:134-141, 1975

15. McNaughton-Filion L, Chen JS, Norton PG: The physician's appearance. Fam Med 23:208-211, 1991

16. Menahem S, Shvartzman P: Is our appearance important to our patients? Fam Pract 15:391-397, 1998

17. Mundinger MO, Kane RL, Lenz ER, et al: Primary care outcomes in patients treated by nurse practitioners or physicians: A randomized trial. JAMA 283:59-68, 2000

18. North RB, Ewend MG, Lawton MT, Kidd DH, Piantadosi S: Failed back surgery syndrome: 5-year follow-up after spinal cord stimulator implantation. Neurosurgery 28:692-699, 1991

19. Otto MW, Dougher M: Sex differences and personality factors in responsivity to pain. Percept Motor Skills 61:383-390, 1985

20. Paice JA, Cohen FA: Validity of a verbally administered numeric rating scale to measure cancer pain intensity. Cancer Nursing 20:88-93, 1997

21. Porzelius J: Memory for pain after nerve-block injections. Clin J Pain 11:112-120, 1995

22. Redelmeier DA, Kahneman D: Patients' memories of painful medical treatments: Real-time and retrospective evaluations of two minimally invasive procedures. Pain 66: 3-8, 1996

23. Rehman SU, Nietert PJ, Cope DW, Kilpatrick AO: What to wear today? Effect of doctor's attire on the trust and confidence of patients. Am J Med 118:1279-1286, 2005

24. Salovey P, Smith AF, Turk DC, Jobe JB, Willis GB: The accuracy of memory for pain: not so bad most of the time. Am Pain Soc 2:184-191, 1993

25. Stone AA, Broderick JE, Kaell AT, DelesPaul PA, Porter LE: Does the peak-end phenomenon observed in laboratory pain studies apply to real-world pain in rheumatoid arthritics? J Pain 1:212-217, 2000

26. Stone AA, Broderick JE, Shiffman SS, Schwartz JE: Understanding recall of weekly pain from a momentary assessment perspective: Absolute agreement, between- and within-person consistency, and judged change in weekly pain. Pain 107:61-69, 2004

27. Stone AA, Schwartz JE, Broderick JE, Shiffman SS: Variability of momentary pain predicts recall of weekly pain: A consequence of the peak (or salience) memory heuristic. Pers Soc Psychol Bull 31:1340-1346, 2005

28. Sutherland HJ, Lockwood GA, Cunningham AJ: A simple, rapid method for assessing psychological distress in cancer patients: Evidence for linear analog scales. J Psychosoc Oncol 7:31-43, 1989

29. Veterans Health Administration Acute Care Strategic Healthcare Group: Pain as the 5th vital sign: take 5. Anonymous 2001

Dynamic Levels of Glutamate within the Insula are Associated with Improvements in Multiple Pain Domains in Fibromyalgia (FM)

Authors: Richard E. Harris PhD[1], Pia C. Sundgren MD PhD[2], Yuxi Pang PhD[2], Michael Hsu MD[3], Myria Petrou MD[2], Seong-Ho Kim MD[1], Samuel A. McLean MD[4], Richard H. Gracely PhD[1], and Daniel J. Clauw MD[1]
Author Addresses: Department of Internal Medicine[1], Department of Radiology[2], Department of Physical Medicine and Rehabilitation[3], and Department of Emergency Medicine[4], The University of Michigan, Ann Arbor Michigan 48109

Corresponding Author:
Richard E. Harris, PhD
Chronic Pain and Fatigue Research Center
24 Frank Lloyd Wright Drive
PO Box 385, Lobby M
Ann Arbor, MI 48106
Phone: (734)-998-6996; Fax: (734)-998-6900
Email: reharris@med.umich.edu

Acknowledgements: Funding for this study came from Department of Army grant DAMD-17/002-0018 and NIH/NCRR grant M01-RR000042. REH was supported by a grant from the NIH/NCCAM K01 AT01111-01. SAM was supported by NIH K12 RR017607-01. We acknowledge Keith Newnham for his expertise in collecting H-MRS spectra. There are no conflicts of interest for any of the authors with the material presented.

Abstract

Objective: Fibromyalgia (FM) is a chronic widespread pain condition that is thought to arise from augmentation of central neural activity. Glutamate (Glu) is an excitatory neurotransmitter that functions in pain processing pathways. We investigated the relationship between changing levels of Glu within the insula of FM patients, and improvements in pain.

Methods: 10 FM patients underwent two proton magnetic resonance spectroscopy (H-MRS) and two functional magnetic resonance imaging (fMRI) sessions, once each before and following a non-pharmacologic intervention to reduce pain. During H-MRS anterior and posterior insular regions were examined separately using single voxel spectroscopy (SVS). Relative levels of Glu and other metabolites were estimated with respect to creatine (Cr; e.g. Glu/Cr). During fMRI, painful pressures were applied to the thumbnail to elicit neuronal activations. Experimental pressure pain thresholds and clinical pain ratings (Short Form of the McGill Pain Questionnaire: SF MPQ) were also assessed prior to each imaging session

Results: Both experimental ($p=0.047$) and clinical (SF MPQ: $p=0.043$) pain were reduced following treatment. Changes in Glu/Cr pre-post treatment were negatively correlated with changes in pressure pain thresholds ($r=-0.95;p<0.001$) and positively correlated with changes in clinical pain (SF MPQ: $r=0.85;p<0.002$). Changes in the fMRI blood oxygen level dependent (BOLD) effect were positively correlated with changes in Glu/Cr within the contralateral insula ($r=0.81;p=0.002$).

Conclusion: Reduction of Glu within the insula is associated with improvements in multiple pain domains in FM. H-MRS may be a useful biomarker and surrogate endpoint for clinical trials in this population.

Fibromyalgia (FM) is a chronic widespread pain disorder afflicting approximately 2-4% of individuals in industrialized countries (1). Although the underlying etiology of this condition is unknown, dysfunction within the central nervous system has been implicated. Results from fMRI (2,3), single photon emission tomography (4), and positron emission tomography (5) support this hypothesis.

One structure that is consistently found to be associated with augmented pain evoked activity in FM is the insula (2,3). In addition to its function in speech, taste, and auditory systems, the insula is also intimately involved in somatosensory and visceral pain processing (6). It is strategically located in a bidirectional pathway between the secondary somatosensory cortex and the amygdala (6). This anatomical position may give the insula a unique regulatory function within the "pain matrix". Topographically the posterior insula is thought to be involved in sensory pain discriminative activities (7), whereas the anterior insula may play a greater role in processing the affective dimension of pain (8).

Glutamate (Glu) is a major excitatory neurotransmitter within the nervous system and is known to function in pain neuropathways. Since elevated Glu levels have been reported in the cerebrospinal fluid of FM patients (9), it is reasonable to suspect that this molecule is involved in the augmented pain transmission observed in FM patients (2,3).

We performed a longitudinal proton magnetic resonance (H-MRS) study to investigate the role of Glu within the insula of FM patients. H-MRS is a non-invasive procedure that can be used to determine the relative concentration of specific brain metabolites *in vivo*. We focused our search on changing levels of Glu following a non-pharmacologic treatment, within both the anterior and posterior insula of FM patients. We hypothesized that changes in Glu should be

positively correlated with clinical pain changes. Conversely changes in Glu levels should be negatively correlated with changes in pressure pain thresholds, since lower thresholds are indicative of greater pain sensitivity. Finally in an exploratory analysis we investigated the relationship between changes in Glu and corresponding variations in pain evoked fMRI BOLD effects.

Methods

Participants

As part of an ongoing study investigating the impact of acupuncture treatment in FM, 10 female patients (mean age=48+/-15yrs) were examined with two H-MRS and two fMRI sessions spaced one month apart. Participants were randomized to receive either nine traditional acupuncture treatments or nine non-skin penetrating sham acupuncture treatments between imaging sessions. All analyses presented here were blinded to treatment assignment, since we were not interested in potential differential effects between acupuncture and sham, but rather whether Glu changes corresponded to changes in pain. All participants gave written informed consent and all study protocols were approved by the University of Michigan Institutional Review Board.

Participants: 1) met the American College of Rheumatology (1990) criteria (10) for the diagnosis of FM for at least 1 year; 2) had pain more than 50% of days; 3) were willing to limit the introduction of new medications or treatment modalities for control of FM symptoms during the study; 4) were between ages 18 and 75; 5) were female; 6) were right handed; and 7) were capable giving written informed consent. Patients were excluded if they: 1) had acupuncture previously; 2) had use of narcotic analgesics or history of substance abuse, 3) had the presence of other diseases that caused pain; 4) had concurrent participation in other therapeutic trials; 5) were pregnant or nursing mothers; 6) had severe psychiatric illnesses; 7) had current major depression; or 8) had contraindications to acupuncture, H-MRS, or fMRI.

Proton Magnetic Resonance Spectroscopy (H-MRS)

All subjects underwent conventional magnetic resonance imaging of the brain on a General Electric 3.0 Tesla MR scanner (GE, Milwaukee, USA). SVS was performed using the following parameters: PRESS, TR 3000ms/TE 30ms, 90 degree flip angle, NEX 8, FOV 16, with a volume of interest (VOI) of 2x2x3cm. During each session, two separate SVS sequences were performed, once with the VOI placed in the right anterior insula and once in the right posterior insula (Figure 1A). The right insula was chosen because it is contralateral to the pressure pain stimulus applied during fMRI. Patients were at rest during both H-MRS sessions. The raw data from each single voxel MR spectroscopy sequence underwent manual post-processing using H-MRS software (LCModel; Oakville, ON, Canada). LCModel uses a linear combination of individual spectra obtained from pure molecular species to fit the experimental spectra (Figure 1B). Values for Glu, glutamine (Gln), and combined Glu+Gln (Glx) were calculated as ratios to the internal standard creatine (Cr; eg. Glu/Cr). Similar calculations were done for other major metabolites including N-acetyl aspartate (NAA), choline compounds (Cho), and myo-inositol (mI; e.g. mI/Cr).

Functional Magnetic Resonance Imaging (fMRI)

Functional MRI scans were acquired on the same 3.0 Tesla scanner. On each scanning day, subjects completed two fMRI runs, acquired with a spiral gradient echo sequence (TR=2500, TE=30, flip angle=90, FOV=22cm). Slices were three mm thick, with an in-plane resolution of 3.125 x 3.125 acquired at 48 locations parallel to the anterior-posterior commissure plane. The first 6 volumes in each run were discarded to allow for T1 equilibration effects. Preprocessing was performed using SPM2 (Wellcome Department of Cognitive Neurology, London, UK) and included correction for slice-acquisition timing to the middle slice (AIR 3.08

routines), realignment to the first volume of each run to correct for intra-scan movement, and smoothing with a Gaussian kernel of 8mm FWHM to compensate for small residual anatomic variations across subjects. Smoothed images were then band pass-filtered (80 sec high pass filter) to eliminate low frequency signals. A general linear model was constructed with parameters corresponding to the type of pressure stimulus applied in each block (either: no touch; innocuous touch; low pain=GBS 0.5; mild pain=GBS 7.5; and moderate pain=GBS 13.5; see below), modeling each run separately. Blocks were 25 sec in duration, and presented according to a fixed pseudorandom paradigm in which every other block consisted of the no-touch condition. To allow for comparison across individuals, one of the three painful pressure blocks was set to $2kg/cm^2$. Each stimulus block was convolved with a canonical hemodynamic response function. Using SPM2, parameter estimates of block-related activity were established for each voxel, and contrast images were calculated by applying a linear contrast of the parameter estimates of the $2kg/cm^2$ pressure versus the no touch condition for each participant and time point. The resulting statistical images for each subject were then spatially normalized into ICBM space by applying the T1-SPGR transformation parameters to the SPM2 contrast image.

Percent differences in BOLD effects, pre-post treatment, were calculated for the entire volume for each individual and correlated with the Glu/Cr change scores in posterior insula (pre-post treatment). Our *a priori* hypothesis was that changes in BOLD activation within the insula would be correlated with changes in Glu/Cr. Therefore we employed an uncorrected statistical threshold of $p<0.001$ with a minimum cluster size of 10 voxels, for clusters identified within the insula. Individual BOLD activations were extracted using the Marsbar region of interest toolbox for SPM2 (version 0.38).

Clinical Pain

Clinical pain was assessed immediately prior to each imaging session with the Short Form of the McGill Pain Questionnaire (SF MPQ; 11). Our analysis focused on the "sensory" dimension of pain assessed by this questionnaire, as its magnitude was reduced with treatment.

Experimental Pain

Pressure pain tenderness was assessed prior to each imaging session (12,13). Briefly, discrete pressure stimuli were applied to the subject's left thumbnail using a stimulation device which eliminates any direct examiner/subject interaction. Pain intensity ratings were recorded on the Gracely Box Scale questionnaire (GBS; 13) using a random presentation paradigm. During the testing, stimulus pressures were determined interactively: a computer program continuously adjusted the stimulus pressures in three pressures stimulus pressures to produce the same response distribution (i.e., GBS=0.5, 7.5, and 13.5) in each subject. We correlated metabolite changes with changes in the mild pain pressure (GBS 7.5), since this threshold increased following treatment.

Statistical Analyses

Metabolite/Cr ratios, percent change in BOLD activations, and pain ratings were entered into SPSS v.14 (Chicago, IL). Due to our small sample size, we performed non-parametric Spearman correlations to determine significant relationships between Glu/Cr levels and changes in pain outcomes. For these correlation analyses, a Bonferroni corrected p-value of 0.0042 was

applied to assign significance to correlations between changes in metabolite ratios (Glu/Cr, Gln/Cr, and Glx/Cr) and changes in pain domains (i.e. 2 brain regions [anterior and posterior insula], 2 pain domains [clinical and experimental], and 3 metabolites; 0.05/12 = 0.0042). A similar correction was performed for the analysis of baseline and post-treatment metabolite ratios within the posterior insula and reductions in pain (i.e. 3 metabolites, 2 time points [baseline and post-treatment], and 2 pain domains [clinical and experimental]; 0.05/12 = 0.0042). Non-parametric Wilcoxon Signed Ranks Tests were performed to determine changes in clinical and evoked pain pre-post treatment.

Results

Following treatment, pressure pain sensitivity was significantly reduced for mildly painful pressures (meandiff(sd):-0.34(0.46)kg;p=0.047), and clinical pain improved for the sensory (meandiff(sd):3.50(4.70);p=0.043) dimension of pain.

Figure 1B depicts a representative spectrum obtained from the posterior insula prior to treatment. A significant negative correlation was detected between Glu/Cr change scores within the posterior insula and changes in pressures required to elicit mild pain (Figure 1C;r=-0.95;p<0.001). Similarly a positive correlation was detected between changes in posterior insular Glu/Cr and changes in clinical pain (Figure 1D;SFMPQ sensory: r=0.85;p=0.002). Greater glutamine (Gln/Cr) levels in the posterior insula *post*-treatment were also associated with more clinical pain reduction (r=0.81;p=0.004).

No significant correlations were detected between change scores in any other posterior insula metabolite ratios (i.e. NAA/Cr, Cho/Cr, or mI/Cr) for either clinical or evoked pain measures (all p>0.10). Also no significant change was detected for Cr concentrations within the posterior insula (p=0.98).

Since there is debate as to whether H-MRS can accurately measure glutamate separately from glutamine within humans at 3 Tesla, we also assessed Glx/Cr levels (i.e. the combination of glutamate and glutamine). Glx/Cr changes within the anterior (r=-0.63;p=0.049) and the posterior insula (r=-0.62;p=0.058) were both negatively correlated with changes in pressure pain, albeit at the trend level. Overall these data are consistent with insular glutamate and/or glutamine being associated with changes in multiple pain domains in FM.

Since glutamate functions in pain neurotransmission, we next correlated changes in Glu/Cr within the right posterior insula with changes in the BOLD responses (pre-post treatment)

elicited by painful pressure applied to the thumbnail bed. Changes in Glu/Cr levels, within the right posterior insula, were positively correlated with changes in BOLD activations within the left posterior insula (Figure 2A left panel;t=6.6;p<0.001 uncorrected;MNI coordinates:x=-42;y=-12;z=0). In contrast a negative correlation was detected for changes in Glu/Cr and changes in BOLD activation in the right posterior insula at the trend level (Figure 2B left panel;t=4.1;p=0.0018 uncorrected;MNI coordinates:x=38 ;y=-14;z=-6).

Discussion

These data are the first evidence of a correlation between changing levels of insular Glu and improvements in FM pain. Since glutamate is a major excitatory neurotransmitter involved in pain transmission, these observations are not unexpected. These data are also consistent with a recent H-MRS study reporting increases in Glu/Cr within the anterior cingulate in response to cold pain within healthy pain free controls (14). However our data show primarily the converse of this relationship, namely reductions in pain are associated with lower Glu/Cr values.

We recognize that detecting Glu specific concentrations accurately at 3 Tesla in humans is difficult due to overlapping proton resonances between Gln and Glu. For this reason, we also investigated combined Glu/Cr and Gln/Cr levels which may be less controversial (14). Again we find that changes in Glx/Cr within the insula are negatively correlated with reduction in pressure pain thresholds. Since we did not detect significant relationships between changes in any other major metabolite and pain improvement, our findings are likely to be specific for Glu and/or Gln.

It is unlikely that our Glu measurements reflect solely synaptic levels of this neurotransmitter, as the volume of brain tissue sampled also included cell bodies and processes of non-neuronal cells. Our measurements probably reflect an average of combined intra- and extracellular Glu arising from both neuronal and non-neuronal cells. A growing body of research over the last decade suggests that the Glu – Gln cycle between astrocytes and neurons may regulate synaptic activity (15). Interestingly, individuals with the greatest pain reduction also showed higher levels of Gln/Cr *post*-treatment suggesting that our treatment intervention may have altered the Glu – Gln cycle.

Consistent with Glu functioning in pain evoked activity, we also detect changes in fMRI BOLD activations which parallel dynamic Glu/Cr levels in the posterior insula. These data are

consistent with augmented neural activity within this region in FM (2,3). However, we find a differential relationship between Glu/Cr within the right posterior insula and changes in BOLD activity within the left and right insula. This observation is unexpected and may reflect that our intervention influenced the left and right insula unequally. Alternatively Glu may influence BOLD activations differentially for task and resting conditions. Exploration of this finding requires additional research.

Due to the small sample sized used in our trial these findings should be interpreted carefully. However our data suggest that Glu may be a useful biomarker for disease severity in FM and future investigations of Glu within FM are warranted.

Reference List

(1) Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995;38(1):19-28.

(2) Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 2002;46(5):1333-1343.

(3) Cook DB, Lange G, Ciccone DS, Liu WC, Steffener J, Natelson BH. Functional imaging of pain in patients with primary fibromyalgia. J Rheumatol 2004;31(2):364-378.

(4) Mountz JM, Bradley LA, Alarcon GS. Abnormal functional activity of the central nervous system in fibromyalgia syndrome. Am J Med Sci 1998;315(6):385-396.

(5) Harris RE, Clauw DJ, Scott DJ, McLean SA, Gracely RH, and Zubieta J-K. Decreased Central μ-Opioid Receptor (MOR) Availability in Fibromyalgia (FM). J Neurosci 2007 *in press*.

(6) Augustine JR. Circuitry and functional aspects of the insular lobe in primates including humans. Brain Res Brain Res Rev 1996;22(3):229-244.

(7) Craig AD, Chen K, Bandy D, Reiman EM. Thermosensory activation of insular cortex. Nat Neurosci 2000;3(2):184-190.

(8) Singer T, Seymour B, O'Doherty J, Kaube H, Dolan RJ, Frith CD. Empathy for pain involves the affective but not sensory components of pain. Science 2004;303(5661):1157-1162.

(9) Sarchielli P, Mancini ML, Floridi A, Coppola F, Rossi C, Nardi K et al. Increased Levels of Neurotrophins Are Not Specific for Chronic Migraine: Evidence from Primary Fibromyalgia Syndrome. J Pain 2007 *in press*.

(10) Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33(2):160-172.

(11) Melzack R. The short-form McGill Pain Questionnaire. Pain 1987;30(2):191-197.

(12) Petzke F, Gracely RH, Park KM, Ambrose K, Clauw DJ. What do tender points measure? Influence of distress on 4 measures of tenderness. J Rheumatol 2003;30(3):567-574.

(13) Petzke F, Harris RE, Williams DA, Clauw DJ, Gracely R.H. Differences in unpleasantness induced by experimental pressure between patients with fibromyalgia and controls. Eur J Pain 2005;9:325-335.

(14) Mullins PG, Rowland LM, Jung RE, Sibbitt WL, Jr. A novel technique to study the brain's response to pain: proton magnetic resonance spectroscopy. Neuroimage 2005;26(2):642-646.

(15) Hertz L, Zielke HR. Astrocytic control of glutamatergic activity: astrocytes as stars of the show. Trends Neurosci 2004;27(12):735-743.

Figure Legends

Figure 1 Changing Levels of Glu/Cr are Associated with Improvements in Pain in FM. A) Axial T1-weighted image showing single voxel placement for (i) posterior and (ii) anterior right insula in H-MRS. B) Representative H-MRS spectrum from the posterior insula fit with LCModel (red trace; * = resonance from two Glu γ proton resonances at 2.35ppm). C) Correlation between changes in Glu/Cr within the posterior insula and changes in mild pressure pain threshold. D) Correlation between changes in Glu/Cr within the posterior insula and changes in clinical pain (SF MPQ sensory score).

Figure 2 Dynamic Levels of Glu/Cr within the Posterior Insula are Associated with Changes in Neural Activity. A) Changes in fMRI BOLD activations within the left insula are positively correlated with changes in Glu/Cr within the right posterior insula (left panel). Scatter plot of individual BOLD and Glu/Cr changes are depicted in the right panel. B) Changes in fMRI BOLD activations within the right insula are negatively correlated with changes in Glu/Cr within the right posterior insula (left panel). Scatter plot of individual BOLD and Glu/Cr changes are depicted in the right panel.

Figure 1

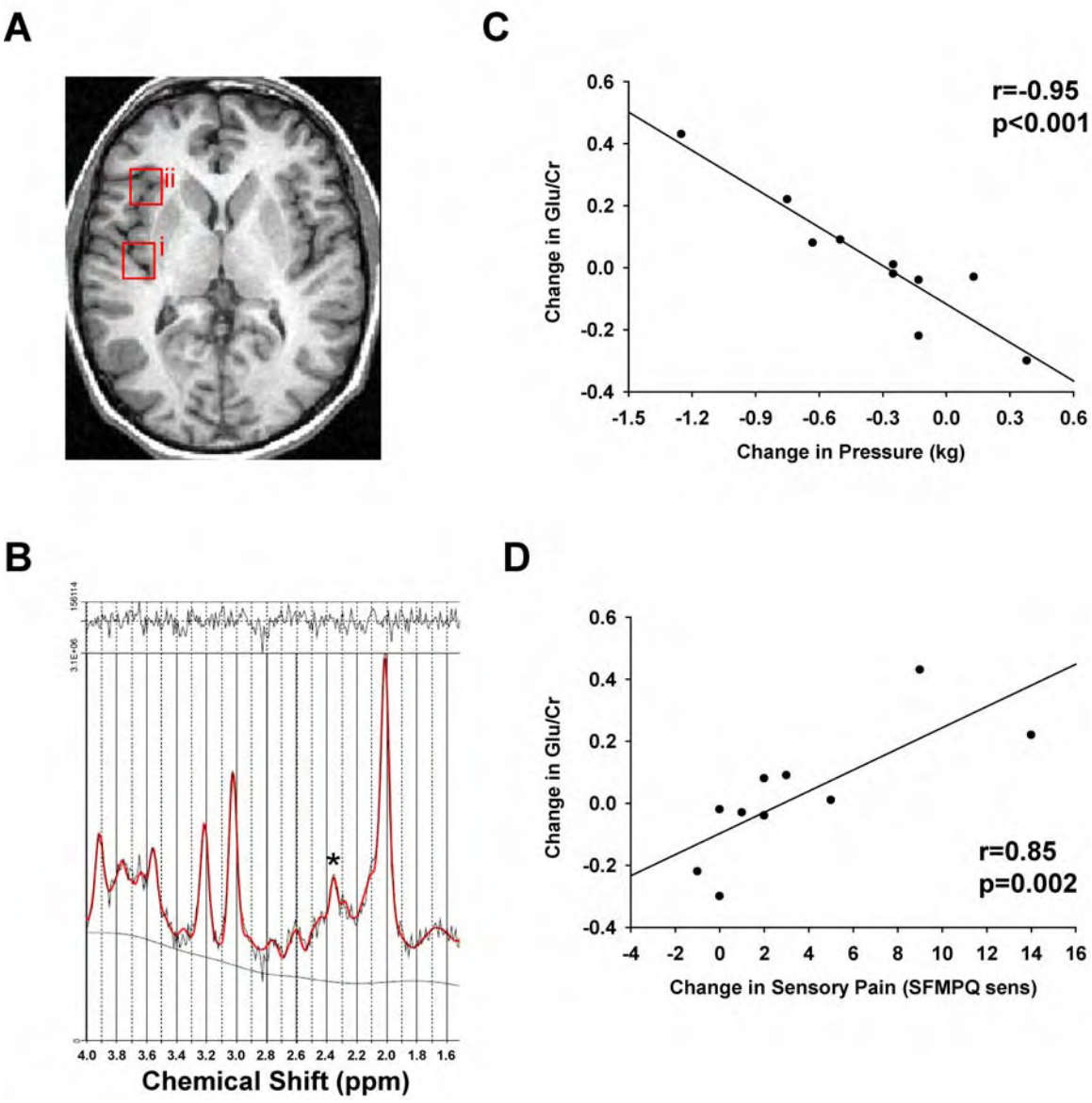
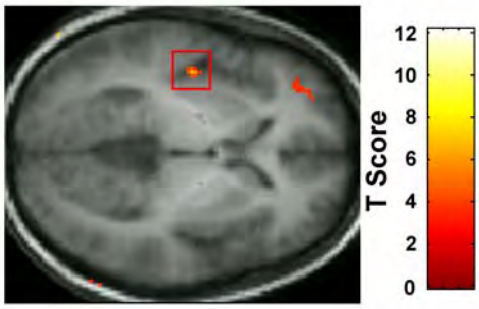
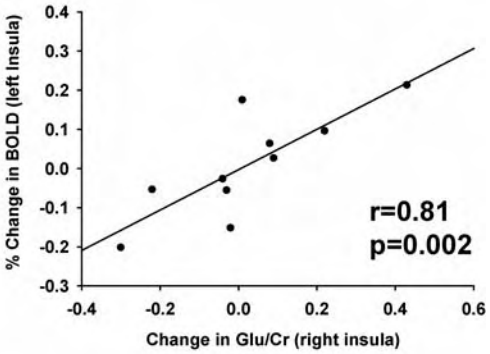

A
ii
i
C
r=-0.95
p<0.001
Change in Glu/Cr
Change in Pressure (kg)
B
*
Chemical Shift (ppm)
D
r=0.85
p=0.002
Change in Glu/Cr
Change in Sensory Pain (SFMPQ sens)

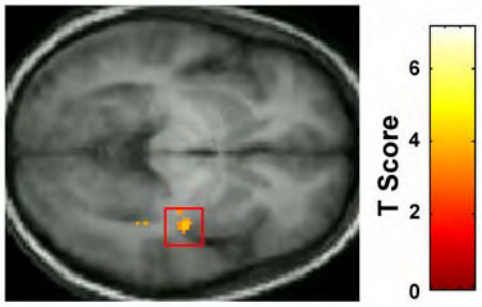
Figure 2

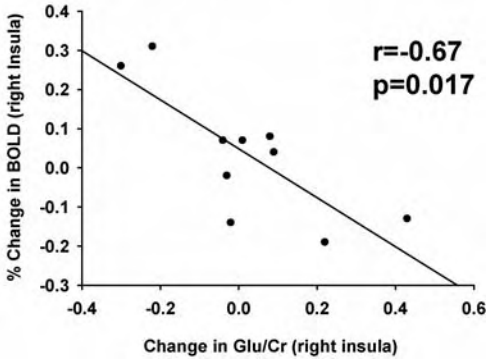
A


T Score
12
10
8
6
4
2
0


% Change in BOLD (left Insula)
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
-0.4
-0.2
0.0
0.2
0.4
0.6
Change in Glu/Cr (right insula)
r=0.81
p=0.002

B


T Score
6
4
2
0


% Change in BOLD (right Insula)
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
-0.4
-0.2
0.0
0.2
0.4
0.6
Change in Glu/Cr (right insula)
r=-0.67
p=0.017

ABSTRACTS 2007

American Pain Society (APS)

26th Annual Scientific Meeting
Washington, DC; May 2 – 5, 2007
(3 abstracts)

American College of Rheumatology (ACR)

71st Annual Scientific Meeting
Boston, MA; November 6 – 11, 2007
(15 abstracts)

American Pain Society

Program Committee
Paper and Poster Abstracts
Faculty List
Conference Overview and Special Events
Program Descriptions
Program Brochure Download
Register Online
Abstracts
Preconference Session
Pediatric Pain Forum
Resident's Course
Special Interest Group Meetings
Young Investigator Travel Support
CE Information
Paperless Meeting
Online Session Recordings
Speaker Information Center
Hotel and Travel Information
Wireless Internet Access
Registration Materials
Enjoying Washington
Exhibits
Corporate Satellite Symposia
Guidelines for Commercially Supported Satellite Symposia
Commercial Support
Advertising Opportunities
Future Meetings
Past Meetings

Annual Meeting

Differential changes in mu-opioid receptor (MOR) availability following acupuncture and sham acupuncture therapy in fibromyalgia (FM) patients

Perform a new search

Year: 2007

Poster #: 692

Title: Differential changes in mu-opioid receptor (MOR) availability following acupuncture and sham acupuncture therapy in fibromyalgia (FM) patients

Authors: R Harris, D Scott,R Gracely,D Clauw,J Zubieta; University of Michigan, Ann Arbor, MI

Classification: Disease Entities (Human)

Themes: C07 - Myofascial Pain & Fibromyalgia

Description:

Multiple lines of evidence implicate MORs in analgesia following placebo and acupuncture treatments. No study has examined the differential effects of these two interventions on binding of central MORs in chronic pain patients. We investigated the relationship between changes in MOR availability following acupuncture and sham acupuncture and subsequent changes in clinical pain. 18 female FM patients (ages 18-75) were randomized to receive either one acupuncture (n=9) or one sham acupuncture (n=9) treatment. Acupuncture treatment involved insertion of 9 sterile single-use acupuncture needles into the body whereas sham treatment did not involve skin penetration. Prior to and during treatment, all subjects underwent a 90 minute 11C-carfentanil positron emission tomography (PET) scan with needle insertion occurring at 40 minutes. Clinical pain was assessed pre- and post-treatment with the Gracely Box Scale (GBS). PET images were processed with Logan plot analysis resulting in maps of whole-brain MOR binding potential (BP). Correlations between changes in clinical pain and MOR BP were performed using SPSS v14.0. The acupuncture group displayed slightly greater reductions in clinical pain, but this was not statistically different between groups (mean difference pre-post+SD: acu=1.4+4.7; sham=0.3+2.8; p=0.54). Within the right inferior insula and right nucleus accumbens, MOR BP increased following acupuncture but not sham acupuncture (BP mean difference pre-post+SD: insula acu=-0.36+0.30, sham=-0.07+0.25; p=0.04; accumbens acu=-0.45+0.52, sham=-0.05+16; p=0.04). Changes in clinical pain were positively correlated with changes MOR BP in the insula (r=0.70; p=0.04) and accumbens (r=0.76; p=0.02) in the acupuncture but not the sham group (insula r=-0.47; p=0.24; accumbens r=0.06; p=0.89). There are differential effects of acupuncture and sham acupuncture on MOR BP in chronic pain patients, and these effects are associated with acupuncture efficacy.

About APS | Membership | The Journal of Pain | APS Bulletin
Publications | Decade of Pain Control and Research | Advocacy and Policy | Awards

For People in Pain | Log In to Members Only Area
Annual Meeting Updates | Abstract Archives | Calendar of Events
Classified and Recruitment Advertising
Links to Related Resources | Who's Who in APS

Annual Meeting

Perform a new search

Paper Session 324

mu-Opioid Receptor (MOR) Binding Predicts Differential Responsiveness to Acupuncture and Sham Acupuncture Therapy in Fibromylagia (FM)

Year: 2007

Poster #: 795

Authors: R Harris,D Scott, M Guevara,R Gracely,J Zubieta,D Clauw; University of Michigan, Ann Arbor, MI

Classification: Treatment Approaches (Physical)

Themes: E01 - Acupuncture

Description:

Controlled clinical trials of acupuncture in FM demonstrate that both sham and real acupuncture are effective at reducing pain. Currently no biological factor has been shown to predict responsiveness to either treatment. Since MORs are implicated in both acupuncture and placebo effects, we investigated the relationship of baseline MOR binding to subsequent pain relief. 18 female FM patients were randomized to receive either one acupuncture or one sham acupuncture treatment. Immediately prior to needle insertion, all subjects underwent a single 40 minute 11C-carfentanil positron emission tomography (PET) scan. Clinical pain was assessed pre- and post-treatment with the Short Form of the McGill Pain Questionnaire (SF-MPQ). PET images were processed with Logan plot analysis resulting in maps of whole-brain MOR binding potential (BP). Since patient expectancies prior to treatment have been associated with placebo effects, we limited our analysis to three brain regions (L caudate, L insula, and L precentral gyrus) that showed significant correlations between MOR BP and expectations of pain relief in all participants. Correlations between changes in SF-MPQ and MOR BP were performed using SPSS v14.0. Both groups displayed clinically meaningful reductions in clinical pain (SF-MPQ total score), but this was not statistically different between groups (mean difference pre-post+SD: acu=4.2+8.9; sham=5.2+5.8; p=0.78). Within the left

insula, individual changes in SF-MPQ total score were negatively correlated with MOR BP pre-treatment for the acupuncture group ($r=-0.76$; $p=0.017$) whereas in the sham group there was a statistically insignificant trend in the opposite direction ($r=0.50$; $p=0.17$). However within the left precentral gyrus, both groups showed similar relationships between MOR BP and changes in affective pain (SF-MPQ affective score; acu: $r=-0.68$, $p=0.04$; sham: $r=-0.64$, $p=0.06$). Baseline levels of MOR binding within the left insula are associated with differential responsiveness to acupuncture treatment. The mechanism of action of this effect remains to be elucidated.

American Pain Society

Program Committee
Paper and Poster Abstracts
Faculty List
Conference Overview and Special Events
Program Descriptions
Program Brochure Download
Register Online
Abstracts
Preconference Session
Pediatric Pain Forum
Resident's Course
Special Interest Group Meetings
Young Investigator Travel Support
CE Information
Paperless Meeting
Online Session Recordings
Speaker Information Center
Hotel and Travel Information
Wireless Internet Access
Registration Materials
Enjoying Washington
Exhibits
Corporate Satellite Symposia
Guidelines for Commercially Supported Satellite Symposia
Commercial Support
Advertising Opportunities
Future Meetings
Past Meetings

Annual Meeting

Relationship between expectation and μ-opioid receptor (MOR) binding prior acupuncture and sham acupuncture treatment in fibromyalgia

Perform a new search

Year: 2007

Poster #: 846

Title: Relationship between expectation and μ-opioid receptor (MOR) binding prior acupuncture and sham acupuncture treatment in fibromyalgia

Authors: M Guevara, D Scott,J Zubieta,D Clauw,R Harris; Chronic Pain and Fatigue Research Center, Ann Arbor, MI

Classification: Treatment Approaches (Psychosocial & Cognitive)

Themes: F09 - Placebo

Description:

Expectation of analgesia is proposed to be a significant factor in placebo effects and has been previously associated with the pain-suppressive endogenous opioid system. Using positron emission tomography (PET), we investigated the relationship between MOR binding and expectations of pain relief prior to treatment within fibromyalgia patients. 18 female patients (ages 18-75) diagnosed with fibromyalgia underwent 11C-carfentanil PET prior to receiving either one acupuncture (n=9) or one sham (n=9) acupuncture treatment. All patients met ACR 1990 criteria for the diagnosis of fibromyalgia for at least 1 year. Expectancies prior to treatment were assessed by asking, "How confident are you that the insertion of acupuncture needles into your body will alleviate your pain?" and using a numerical rating scale 0 (not confident) – 100 (extremely confident). MOR binding was determined by 11C-carfentanil PET prior to treatment. Images were processed with Logan plot analysis resulting in maps of whole-brain MOR binding potential (BP). MOR binding within specific brain regions was correlated with patient expectations using SPM99. Additional correlations between expectancies for pain relief and MOR BP from identified regions were performed using SPSS v14.0. The mean and standard deviation for expectations were 53.89 and 13.78 respectively. Significant positive correlations between expectancy for pain relief and MOR BP were detected in the insula (r=0.677;p=0.001) and the temporal cortex (r=0.593;p=0.005). MOR BP within the left caudate demonstrate a trend to negative correlation with expectancy for pain relief (r=-0.393;p=-0.053). These data indicate that expectations for pain relief are associated with differential MOR binding prior to treatment. Effects of expectations on placebo analgesia may be mediated in part by the effects of endogenous opioids and the concentration of MOR's in these regions.

About APS | Membership | The Journal of Pain | APS Bulletin
Publications | Decade of Pain Control and Research | Advocacy and Policy | Awards

For People in Pain | Log In to Members Only Area
Annual Meeting Updates | Abstract Archives | Calendar of Events
Classified and Recruitment Advertising
Links to Related Resources | Who's Who in APS
International and Regional Societies

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

Print this Page for Your Records Close Window

Control/Tracking Number: 07-A-2360-ACR
Activity: ACR Abstract Submission
Current Date/Time: 9/12/2007 10:42:41 AM

Increased Frequency of the Minor Allele for beta-3 Adrenergic Receptors in Individuals with Fibromyalgia and Related Syndromes

Author Block: Daniel J. Clauw[1], Inna Belfer[2], Mitchell Max[2], David A. Williams[1], Richard H. Gracely[1], Samuel A. McLean[3], Richard E. Harris[1], Andi Neely[4], Eric Bair[4], Luda Diatchenko[4], William Maixner[4]. [1]Rheumatology, University of Michigan, Ann Arbor, MI; [2]NIH, NIDCR, Bethesda, MD; [3]Emergency Medicine, University of Michigan, Ann Arbor, MI; [4]Center for Sensory Disorders, UNC-Chapel Hill, Chapel Hill, NC

Abstract:
Introduction. Previous studies have demonstrated that there is a very strong familial predisposition to develop FM, with first degree relatives of FM patients 8X as likely to develop this as controls (Arnold, 2004). To date, a few studies have identified specific genetic polymorphisms that were more commonly seen in FM than control groups, but most of the associations identified thus far have been weak or inconsistent. Because of the strong evidence that autonomic dysfunction may play a role in both FM and other related chronic somatic syndromes such as chronic fatigue syndrome (CFS), and Gulf War Illnesses (GWI), we performed a preliminary study examining the rate of polymorphisms involving candidate genes involved in catecholamine synthesis or action, including catecholamine-O-methyltransferase, and beta-2 or 3 adrenergic receptors (B2AR, B3AR).
Methods: Genetic analyses of known polymorphisms in COMT and beta-2 and -3 adrenergic receptors were performed on archival samples from 46 well-characterized patients with chronic multisymptom illnesses (CMI) such as FM, CFS, and GWI, and 40 matched controls. After examining whether the polymorphisms were unevenly distributed between patients and controls, secondary analyses were performed looking for associations with levels of symptoms, measures of evoked pain sensitivity, and measures of both autonomic and hypothalamic pituitary adrenal function.
Results: Although in this small sample there were no statistically significant differences in the incidence of polymorphisms in the COMT or B2AR alleles, there was a difference in the distribution of B3AR alleles between groups, with those who were heterozygous for the minor allele more likely to have CMI (OR = 4, p=.04). Heterozygotes for the minor allele also had more severe clinical pain measured using a variety of scales (VAS, p=.008; Present Pain Intensity, p = .02), and more pronounced hyperalgesia (to both heat [p=.007] and pressure [p = .06]).
Conclusion: These data suggest a fairly strong association between possessing the minor allele for B3AR and the presence of CMI such as FM, CFS, and GWI. In addition, possessing this allele is independently associated with pain intensity and measures of hyperalgesia in the combined groups, suggesting it may be particularly involved in augmented pain transmission. These results need to be replicated in larger samples.
:

Author Disclosure Information: **D.J. Clauw**, Department of Defense, Cooperative Agreement, 2; Cypress BioScience, 5; Lilly, 5; Forest, 5; Pfizer, 5; Wyeth, 5; **I. Belfer**, None; **M. Max**, None; **D.A. Williams**, NIH, 2; Cypress BioScience, 5; **R.H. Gracely**, Cypress BioScience, 5; Pierre Fabre, 5; **S.A. McLean**, None; **R.E. Harris**, None; **A. Neely**, None; **E. Bair**, None; **L. Diatchenko**, None; **W. Maixner**, None.

Category (Complete): 9. Fibromyalgia and soft tissue disorder
Keywords (Complete): genetic research ; fibromyalgia ; pain
Additional Keyword (Complete):
Eligibility (Complete):
***Has the data contained in the submitted abstract been presented or accepted for presentation at another meeting prior to the ACR submission deadline of May 3?** : No

Presentation Preference (Complete): Oral or Poster
Payment (Complete): Your credit card order has been processed on Wednesday 2 May 2007 at 1:12 PM.
Status: Complete

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

Print this Page for Your Records Close Window

Control/Tracking Number: 07-A-820-ACR
Activity: ACR Abstract Submission
Current Date/Time: 9/12/2007 10:50:08 AM

Effects of Sleep Restriction and Exercise Deprivation on Mood, Pain, Fatigue, Somatic Symptoms and Cognition in Healthy Adults

Author Block: Jennifer M. Glass, Angela K. Lyden, Cathryn J. Byrne-Dugan, Kim H. Groner, Kirsten R. Ambrose, Peter J. Grace, Dave A. Williams, Richard H. Gracely, Daniel J. Clauw. Rheumatology, University of Michigan, Ann Arbor, MI

Abstract:
Introduction. It is known that good sleep hygiene and regular exercise can improve FM symptoms. We hypothesized that disrupted sleep and exercise routines may be part of the etiology of chronic FM symptoms. Individually, sleep or exercise deprivation can result in increased symptoms of pain, negative mood, fatigue, and dyscognition. In this study, we examined the independent and combined effects of exercise deprivation and sleep restriction in healthy, regularly exercising adults. *Methods.* Eighty-three participants who regularly ran at least 5 times per week and who slept 7-9 hours per night took part in the study. Participants were randomly assigned to one of four groups: control (normal activity and sleep), exercise deprivation, sleep restriction (6 contiguous hours in bed per night), or both exercise and sleep restriction. The deprivation period lasted 10 days. Symptoms were assessed at baseline and near the end of the deprivation period. Symptom domains included pain (self-report and evoked pressure pain sensitivity), fatigue, mood, and dyscognition (self-report and performance measures). Each symptom domain was analyzed with a 2 (pre- and post-deprivation) by 2 (sleep) by 2 (exercise) ANOVA to assess main effects and interaction between sleep restriction and exercise deprivation. *Results.* There was a significant main effect of sleep for all symptom domains. For example, McGill VAS pain increased ($F(1, 80) = 8.794$, $p = .004$), fatigue increased ($F(1,80)=37.00$, $p < .001$), negative mood increased ($F(1,80)=13.41$, $p < .001$), and dyscognition increased ($F(1,80) = 10.98$, $p = .001$). Exercise deprivation had more limited effects on pressure pain sensitivity ($F(1, 80) = 9.93$, $p =.003$), fatigue ($F(1, 80) = 5.97$, $p = .019$) and negative mood ($F(1, 80) = 5.28$, $p = .028$. Surprisingly, there were no significant interactions between sleep and exercise. *Conclusions.* Among healthy regularly exercising and sleeping individuals, disruption of a normal routine was associated with increased pain, fatigue, negative mood, and dyscognition. Sleep restriction produced more widespread and severe symptoms than exercise deprivation.
:

Author Disclosure Information: **J.M. Glass**, None; **A.K. Lyden**, None; **C.J. Byrne-Dugan**, None; **K.H. Groner**, None; **K.R. Ambrose**, None; **P.J. Grace**, None; **D.A. Williams**, NIH, 2; Cypress BioScience, 5; **R.H. Gracely**, Pierre Fabre, 5; Cypress BioScience, 5; **D.J. Clauw**, Department of Defense, Cooperative Agreement, 2; Cypress BioScience, 5; Lilly, 5; Forest, 5; Pfizer, 5; Wyeth, 5.

Category (Complete): 9. Fibromyalgia and soft tissue disorder
Keywords (Complete): exercise ; environmental factors
Additional Keyword (Complete):
Eligibility (Complete):
***Has the data contained in the submitted abstract been presented or accepted for presentation at another meeting prior to the ACR submission deadline of May 3?** : No

Presentation Preference (Complete): Oral or Poster
Payment (Complete): Your credit card order has been processed on Friday 27 April 2007 at 2:32 PM.
Status: Complete

American College of Rheumatology
1800 Century Place, Suite 250
Atlanta, GA 30345
For technical support, email support@abstractsonline.com or call 217-398-1792

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

Print this Page for Your Records Close Window

Control/Tracking Number: 07-A-1087-ACR
Activity: ACR Abstract Submission
Current Date/Time: 9/12/2007 10:46:23 AM

Baseline Heart Rate Variability Predicts Changes in Pain and Cognition, but not Mood or Fatigue after Exercise and Sleep Restriction

Author Block: Jennifer M. Glass, Angela K. Lyden, Cathryn J. Byrne-Dugan, Kim H. Groner, Kirsten R. Ambrose, Richard H. Gracely, David A. Williams, Daniel J. Clauw. Rheumatology, University of Michigan, Ann Arbor, MI

Abstract:
Introduction. Chronic pain disorders such as fibromyalgia (FM) are often precipitated by a “stressful” event (e.g., motor vehicle accident, infection) that prevents normal sleep and exercise. We have hypothesized that many “stressors” may lead to sleep restriction and exercise deprivation, and that this can then lead to increased symptoms of pain, negative mood, fatigue and dyscognition. Furthermore, we have hypothesized that not all individuals are equally susceptible to this phenomenon, and that neurobiological factors can predict if an otherwise healthy individual will respond to such stress with an acute increase in somatic symptoms.
Method. 83 participants who regularly ran at least 5 times per week and who slept 7-9 hours per night took part in the study. Participants were randomly assigned to one of four groups: control (normal activity and sleep), exercise deprivation, sleep restriction (6 contiguous hours in bed per night), or both exercise and sleep restriction. The deprivation period lasted 10 days. Symptoms were assessed at baseline and near the end of the deprivation period. Symptom domains included pain (self-report and evoked pressure pain sensitivity), fatigue, mood, and dyscognition (self-report and performance measures). Autonomic nervous system function was assessed via heart rate variability (HRV) just before the deprivation period. Pearson product moment correlations were calculated (for the participants assigned to a deprivation condition) to assess the association between baseline HRV measures and changes in symptoms pre to post deprivation.
Results. Confirming our preliminary findings, several baseline HRV parameters were strongly correlated with increased symptoms. Total power, very low frequency (VLF) and ultra low frequency (ULF) were related to self-report pain (e.g., $r=-.568$, $p < .001$), high frequency (HF) HRV was related to evoked pressure pain threshold ($r=.369$, $p <.04$), and total power, ULF, HF and HF to LF ratio were related to cognitive function (e.g., $r=-.357$, $p < .05$). None of the HRV parameters were correlated with increased symptoms of negative mood or fatigue.
Conclusions. Amongst a group of healthy, symptom-free individuals, baseline neuro-physiological measures (HRV) predict subsequent symptom development. These data are consistent with the view that the abnormal autonomic nervous system function observed in FM may in part represent a diathesis that predisposes individuals to development of pain and cognitive symptoms after exposure to a stressor.
:

Author Disclosure Information: **J.M. Glass**, None; **A.K. Lyden**, None; **C.J. Byrne-Dugan**, None; **K.H. Groner**, None; **K.R. Ambrose**, None; **R.H. Gracely**, Cypress BioScience, 5; Pierre Fabre, 5; **D.A. Williams**, NIH, 2; Cypress BioScience, 5; **D.J. Clauw**, Department of Defense, Cooperative Agreement, 2; Cypress BioScience, 5; LIlly, 5; Forest, 5; Pfizer, 5; Wyeth, 5.

Category (Complete): 9. Fibromyalgia and soft tissue disorder

Keywords (Complete): exercise ; pain ; physical activity
Additional Keyword (Complete):
: autonomic nervous system

Eligibility (Complete):
***Has the data contained in the submitted abstract been presented or accepted for presentation at another meeting prior to the ACR submission deadline of May 3?** : No

Presentation Preference (Complete): Oral or Poster
Payment (Complete): Your credit card order has been processed on Friday 27 April 2007 at 2:31 PM.
Status: Complete

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

Print this Page for Your Records Close Window

Control/Tracking Number: 07-A-2119-ACR
Activity: ACR Abstract Submission
Current Date/Time: 9/12/2007 10:51:17 AM

Variation in Glutamate and Glutamine Levels within the Inslula are associated with Improvements in Working Memory in Fibromyalgia (FM)

Author Block: Jennifer M. Glass[1], Richard C. Harris[1], Pia C. Sundgren[2], Yuxi Pang[2], Richard H. Gracely[1], Daniel J. Clauw[1]. [1]Rheumatology, University of Michigan, Ann Arbor, MI; [2]Radiology, University of Michigan, Ann Arbor, MI

Abstract:
Purpose: The insular cortex is involved in processing both sensory and affective aspects of pain and more generally is believed to integrate sensory and affective information. Additionally, the insula is involved in language processing, particularly the articulatory loop that is part of the working memory system, and FM patients show working memory impairments. Previous functional neuroimaging studies suggest augmented neural activity within this structure in FM patients. Since glutamate (Glu) is a major excitatory neurotransmitter within the central nervous system, we used proton magnetic resonance spectroscopy (H-MRS) to investigate variations in Glu and glutamine (Gln) levels over time in FM patients. We hypothesized that changes in Glu and/or Gln should parallel improvements in working memory performance.
Methods: As part of an ongoing trial of acupuncture in FM, 10 patients (48+/- 15 yrs) underwent H-MRS prior to and following nine treatments. Single voxel spectroscopy (SVS) was performed using the following parameters: PRESS, TR 3000ms/TE 30ms, 90 degree flip angle, NEX 8, FOV 16, with a volume of interest (VOI) of 2x2x3cm voxel. Two separate SVS sequences were performed with the VOI placed first in the anterior and then the posterior insula. Patients were at rest during each session. Spectra were analyzed offline with LCModel. Values for Glu, Gln, and combined Glu+Gln (Glx) were calculated as ratios to the internal standard creatine (Cre; eg. Glu/Cre). Working memory was assessed pre- and post-treatment with the Letter-Number span test from the Wechsler Memory Scale. Data were analyzed with SPSS v.14.
Results: Working memory performance improved post-treatment. Glu/Cre, Gln/Cre, and Glx/Cre levels did not significantly change over time (all $p>0.05$). Differences in Gln/Cre (pre-post treatment) within the posterior insula were negatively correlated with changes in working memory (Gln/Cre: $r=-0.778$, $p=0.008$). Changes in Glx/Cre levels within the anterior insula were positively correlated with changes in working memory ($r=0.701$, $p=0.024$).
Conclusion: Changes in Insular Glu and/or Gln to Cre ratios correlate with improvements in working memory within FM patients. Specifically, increased Gln/Cre ratio in the anterior insula were associated with larger improvements in working memory. This could result from changes in glutamatergic neurotransmission within the part of the insula that is involved in the articulatory loop. In contrast, decreased ratio of Glx/Cre in the posterior insula were associated with larger improvements in working memory, perhaps due to decreased affective interference. These data are the first to associate Glu and Gln levels with working memory function in FM. H-MRS may be a useful outcome measure in clinical trials within this population.
:

Author Disclosure Information: **J.M. Glass**, None; **R.C. Harris**, Pfizer, Investigator-initiated, 2; **P.C. Sundgren**, None; **Y. Pang**, None; **R.H. Gracely**, Cypress BioScience, 5; Pierre Fabre, 5; **D.J. Clauw**, Department of Defense, Cooperative Agreement, 2; Cypress BioScience, 5; Pfizer, 5; Lilly, 5; Forest, 5; Wyeth,

5.

Category (Complete): 9. Fibromyalgia and soft tissue disorder
Keywords (Complete): cognitive dysfunction ; imaging techniques
Additional Keyword (Complete):
Eligibility (Complete):
***Has the data contained in the submitted abstract been presented or accepted for presentation at another meeting prior to the ACR submission deadline of May 3?** : No

Presentation Preference (Complete): Oral or Poster
Payment (Complete): Your credit card order has been processed on Wednesday 2 May 2007 at 8:48 AM.
Status: Complete

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

Print this Page for Your Records Close Window

Control/Tracking Number: 07-A-1094-ACR
Activity: ACR Abstract Submission
Current Date/Time: 9/12/2007 10:43:38 AM

Working Memory in Fibromyalgia Patients: Impaired Function Caused by Distracting Information, Not Rapid Decay of Stored Information

Author Block: Jennifer M. Glass[1], Denise C. Park[2], Leslie J. Crofford[3], Daryl Fougnie[4], Daniel J. Clauw[1]. [1]Rheumatology, University of Michigan, Ann Arbor, MI; [2]Beckman Institute, University of Illinois, Urbana-Champaign, IL; [3]Rheumatology, University of Kentucky, Louisville, KY; [4]Vanderbilt University, Nashville, TN

Abstract:
Purpose: Self-report of impaired cognition is a common symptom in FM. Previous work using laboratory and neuropsychological measures has shown impairment in working memory, a neurocognitive memory system that simultaneously stores and manipulates a small amount of information for a short period, such as occurs in mental arithmetic. The deficits observed in working memory in FM may be due to faster loss of information (decay), or inability to manage the contents of working memory. In this study we tested whether faster decay from working memory occurs in FM patients.
Methods: Subject groups included FM patients (n=28) and age- and education-matched controls (n=14). Decay from working memory was measured with a computerized consonant-trigram memory test. Three consonants were presented for memorization. Following a brief delay, subjects recalled the trigram by typing them on the keyboard. The delay could range from 0 seconds to 10 seconds. To prevent rehearsal of the consonant trigrams, the delay period was filled with a counting task. The counting task also served as a source of distraction during short-term memory storage.
Results: FM patients had lower recall overall ($F(1, 40) = 8.88$, $p = .005$). Both groups recalled less as the delay period increased ($F(5, 36) = 10.12$, $p < .001$). However, the group by delay interaction was not significant ($F(5, 36) = 1.64$, $p = .175$), indicating that the rate of information loss or decay was no faster in the FM group than the control group.
Conclusions: The results extend previous research showing working memory deficits in FM compared to healthy controls, and indicate that difficulty managing competing or distracting information is the root of working memory problems in FM, rather than a more rapid loss of information from working memory. Since working memory is an important component of higher-order cognitive function, the effects seen here could have much larger impact on patients in hectic environments where there are heavy demands on working memory.
:

Author Disclosure Information: **J.M. Glass**, None; **D.C. Park**, None; **L.J. Crofford**, None; **D. Fougnie**, None; **D.J. Clauw**, None.

Category (Complete): 9. Fibromyalgia and soft tissue disorder
Keywords (Complete): cognitive dysfunction
Additional Keyword (Complete):
Eligibility (Complete):
***Has the data contained in the submitted abstract been presented or accepted for presentation at another meeting prior to the ACR submission deadline of May 3?** : No

Presentation Preference (Complete): Oral or Poster
Payment (Complete): Your credit card order has been processed on Friday 27 April 2007 at 2:51 PM.
Status: Complete

American College of Rheumatology
1800 Century Place, Suite 250
Atlanta, GA 30345
For technical support, email support@abstractsonline.com or call 217-398-1792

Control/Tracking Number: 07-A-949-ACR
Activity: ACR Abstract Submission
Current Date/Time: 9/12/2007 10:41:49 AM

Variation in Glutamate and Glutamine Levels within the Insula are Associated with Improvements in Clinical and Experimental Pain in Fibromyalgia (FM)

Author Block: Richard H. Harris[1], Pia C. Sundgren[2], Yuxi Pang[2], Najma Khatri[1], Richard H. Gracely[1], Daniel J. Clauw[1]. [1]Rheumatology, University of Michigan, Ann Arbor, MI; [2]Radiology, University of Michigan, Ann Arbor, MI

Abstract:
Purpose: The insula is involved in processing both sensory and affective aspects of pain. Previous functional neuroimaging studies suggest augmented neural activity within this structure in FM patients. Since glutamate (Glu) is a major excitatory neurotransmitter within the central nervous system, we used proton magnetic resonance spectroscopy (H-MRS) to investigate variations in Glu and glutamine (Gln) levels over time in FM patients. We hypothesized that reductions in Glu and/or Gln should parallel improvements in clinical pain and evoked pain sensitivity.
Methods: As part of an ongoing trial of acupuncture in FM, 10 patients (48+/- 15 yrs) underwent H-MRS prior to and following nine treatments. Single voxel spectroscopy (SVS) was performed using the following parameters: PRESS, TR 3000ms/TE 30ms, 90 degree flip angle, NEX 8, FOV 16, with a volume of interest (VOI) of 2x2x3cm voxel. Two separate SVS sequences were performed with the VOI placed first in the anterior and then the posterior insula. Patients were at rest during each session. Spectra were analyzed offline with LCModel. Values for Glu, Gln, and combined Glu+Gln (Glx) were calculated as ratios to the internal standard creatine (Cre; eg. Glu/Cre). Clinical and experimental pain were assessed pre- and post-treatment, with the Short Form of the McGill Pain questionnaire (SF-MPQ) and psychophysical pressure pain testing (multiple random staircase) respectively. Data were analyzed with SPSS v.14.
Results: Clinical pain improved over the course of treatment for the sensory but not the affective dimension of pain (SF-MPQ Mean Diff(SD): Sensory=3.5(4.7); p=0.04; Affective=0.1(2.5); p>0.05). Hyperalgesia was also significantly reduced at moderate pressures (Mean Diff(SD)=-0.34(0.46)kg; p=0.04). Glu/Cre, Gln/Cre, and Glx/Cre levels did not significantly change over time (all p>0.05), but differences in Glx/Cre and Glu/Cre (pre-post treatment) within the posterior insula were negatively correlated with changes in hyperalgesia (Glx/Cre: r=-0.68; p=0.03; Glu/Cre: r=-0.93; p<0.001). Changes in Glx/Cre levels within the anterior insula were also negatively correlated with changes in hyperalgesia (r=-0.77; p=0.04). Inter-individual variations in Glu/Cre within the posterior insula were also positively correlated with changes in clinical pain (McGill total: r=0.80; p=0.005; Sensory: r=0.77; p=0.009; Affective: r=0.78; p=0.008).
Conclusion: Insular Glu and/or Gln levels appear to change with improvements in multiple pain dimensions within FM patients. This could result from changes in glutamatergic neurotransmission within this structure. H-MRS may be a useful outcome measure in clinical trials within this population.
:

Author Disclosure Information: **R.H. Harris**, Pfizer, investigator-initiated, 2; **P.C. Sundgren**, None; **Y. Pang**, None; **N. Khatri**, None; **R.H. Gracely**, Pierre Fabre, 5; Cypress BioScience, 5; **D.J. Clauw**, Department of Defense, Cooperative Agreement, 2; Cypress BioScience, 5; Lilly, 5; Forest, 5; Pfizer, 5; Wyeth, 5.

Category (Complete): 9. Fibromyalgia and soft tissue disorder
Keywords (Complete): fibromyalgia ; pain ; neuroimaging
Additional Keyword (Complete):
Eligibility (Complete):
***Has the data contained in the submitted abstract been presented or accepted for presentation at another meeting prior to the ACR submission deadline of May 3?** : No

Presentation Preference (Complete): Oral or Poster
Payment (Complete): Your credit card order has been processed on Thursday 26 April 2007 at 2:59 PM.
Status: Complete

Control/Tracking Number: 07-A-953-ACR
Activity: ACR Abstract Submission
Current Date/Time: 9/12/2007 10:50:40 AM

Differential Sustained Changes in μ-Opioid Receptor (MOR) Availability Following Acupuncture and Sham Acupuncture Therapy in Fibromyalgia (FM)

Author Block: Richard E. Harris[1], Jon-Kar Zubieta[2], David J. Scott[2], Laura Mayo-Bond[1], Richard H. Gracely[1], Daniel J. Clauw[1]. [1]Rheumatology, University of MI, Ann Arbor, MI; [2]Molecular & Behavioral Neuroscience, University of MI, Ann Arbor, MI

Abstract:
Purpose: Clinical trials of acupuncture versus sham therapy in fibromyalgia (FM) have had equivocal findings, suggesting that acupuncture may work via placebo mechanisms. Since μ-opioid receptors (MORs) are thought to be involved in both acupuncture analgesia and placebo effects, we explored long-term changes in central MOR availability using positron emission tomography (PET) in FM. We hypothesized that if traditional acupuncture and sham acupuncture work via the same mechanism, similar changes in MOR availability should be observed between groups.
Methods: 17 female FM patients (45+/-14yrs) were randomized to receive either nine traditional acupuncture (TA; n=9) or nine sham acupuncture (SA; n=8) treatments over the course of 4 weeks. TA involved insertion of 9 acupuncture needles into the body whereas SA did not involve skin penetration. The first and the ninth treatment occurred during PET imaging with ^{11}C-carfentanil, a selective MOR agonist. Each PET session lasted 90 minutes and included a 0-40 minute baseline scan prior to needle insertion. For the purposes of this analysis we compared changes in baseline scans from the first to the second PET session between groups. PET images were processed with Logan plot analysis resulting in maps of whole-brain MOR binding potential (BP; a measure of receptor availability). Images were analyzed with SPM99. Clinical pain was assessed before the first treatment and after the last with the Short Form McGill Pain Questionnaire (SF-MPQ). Correlations between changes in clinical pain and changes in the MOR BP were performed.
Results: Clinically significant improvements in pain were obtained following treatment (SF MPQ total: MeanDiff(SD) TA=5.4(9.6); SA=2.3(6.4)) although there was no between-group difference (p=.44). However significant changes in MOR BP were detected between TA and SA within 17 different brain regions (all $p<0.001$; uncorrected). These regions included: insula, amygdala, thalamus, cingulate (anterior and perigenual), caudate, prefrontal cortex, and hypothalamus. Within the anterior cingulate (ACC) improvements in clinical pain were positively correlated with increases MOR BP for TA (ACC: r=.68; p=.04) but negatively for SA (r=-.81; p=.02). Within the caudate improvements in clinical pain were positively correlated with increases in MOR BP for TA (r=.75; p=.02) but not SA (r=-.02; p=.96). Conversely, within the perigenual cingulate (pgCC) and dmPFC, improvements in clinical pain were associated with decreases in MOR BP for SA (pgCC: r=-.70; p=.05; dmPFC: r=-.73; p=0.04) but not for TA (pgCC: r=.35; p=.35; dmPFC: r=.33; p=.39).
Conclusions: The underlying mechanisms of TA and SA are not equivalent, despite similar results in clinical pain report. Further studies using larger samples will be necessary to corroborate these findings.
:

Author Disclosure Information: **R.E. Harris**, Pfizer, Investigator-initiated, 2; **J. Zubieta**, None; **D.J. Scott**, None; **L. Mayo-Bond**, None; **R.H. Gracely**, Pierre Fabre, 5; Cypress BioScience, 5; **D.J. Clauw**, Cypress BioScience, 5; Lilly, 5; Forest, 5; Pfizer, 5; Wyeth, 5.

Category (Complete): 9. Fibromyalgia and soft tissue disorder
Keywords (Complete): positron emission tomography (PET) ; acupressure/acupuncture ; opioids
Additional Keyword (Complete):
Eligibility (Complete):
***Has the data contained in the submitted abstract been presented or accepted for presentation at another meeting prior to the ACR submission deadline of May 3?** : No

Presentation Preference (Complete): Oral or Poster
Payment (Complete): Your credit card order has been processed on Thursday 26 April 2007 at 3:22 PM.
Status: Complete

Control/Tracking Number: 07-A-1097-ACR
Activity: ACR Abstract Submission
Current Date/Time: 9/12/2007 10:38:34 AM

Catastrophizing and Fatigue are Associated with Poorer Perceived Physical Function Relative to Objective Activity Measures in Fibromyalgia

Author Block: Michael C. Hsu[1], Michael E. Geisser[1], Angela K. Lyden[2], David A. Williams[2], Daniel J. Clauw[2]. [1]Phys Med & Rehab, University of Michigan, Ann Arbor, MI; [2]Rheumatology, University of Michigan, Ann Arbor, MI

Abstract:
Purpose: Patients with fibromyalgia (FM) have low levels of self-reported physical function, compared to either controls or other chronic illnesses. We have previously shown that in both FM patients and controls, there are poor relationships between self-reported function, and objective activity levels as measured by actigraphy. This study examined the potential reasons for the differences between self-reported function and activity levels in FM by examining the symptoms and psychological factors most strongly associated with these discrepanices.
Methods: 31 patients with FM (43.1 ± 8.2 years, 71% women) completed 5 days of ambulatory monitoring of physical activity, using a wristwatch-sized omni-directional accelerometer (Actiwatch-Score). Activity counts were recorded continuously and summed over 5-min epochs. Peak and average activity were defined as the peak and average activity count over all epochs, respectively. Self-reported physical function was measured using the SF36 physical functioning subscale (PF) after completion of the 5-day period. Measures of fatigue (Multidimensional Fatigue Inventory), catastrophizing (Coping Strategies Questionnaire, Catastrophizing subscale), depression (CES-D), anxiety (State-Trait Personality Inventory, Trait Anxiety subscale) and pain (McGill Pain Questionnaire) were also assessed. Data were analyzed using SPSS v.14. Discrepancies between activity (peak and average) and PF scores were calculated as the difference between normalized values, and Pearson's correlation coefficients were obtained among all variables. Simultaneous linear regression models were created to predict peak activity, average activity, and discrepancies between these measures and PF scores; all other variables with significance of correlation < .50 were used as independent variables. Hierarchical regression models were created to check for co-linearity.
Results: SF36 PF scores did not correlate with either peak or average activity ($p = .48$ and .15, respectively). Catastrophizing ($r = .529$, $p < .01$) and fatigue ($r = .521$, $p < .01$) significantly correlated with the degree to which average activity exceeded PF score. Catastrophizing ($r = .404$, $p < .05$) and fatigue ($r = .423$, $p < .05$) also correlated with the degree to which peak activity exceeded PF score. The linear regression model for predicting discrepancy between average activity and PF score was significant ($R^2 = .632$, $p = .002$), and co-linearity was not observed between fatigue and catastrophizing. These discrepancies did not correlate with levels of pain, depression, and anxiety.
Conclusion: Measures of self-reported physical function using the SF36 PF do not correlate with objective measures of activity in FM patients. Higher levels of fatigue and catastrophizing are independently associated with poorer perceived function compared to actigraphy.
:

Author Disclosure Information: **M.C. Hsu**, None; **M.E. Geisser**, None; **A.K. Lyden**, None; **D.A. Williams**, NIH, 2; Cypress BioScience, 5; **D.J. Clauw**, Department of Defense, Cooperative Agreement, 2; Cypress BioScience, 5; Lilly, 5; Forest, 5; Pfizer, 5; Wyeth, 5.

Category (Complete): 9. Fibromyalgia and soft tissue disorder
Keywords (Complete): psychosocial factors ; physical function
Additional Keyword (Complete):
Eligibility (Complete):
***Has the data contained in the submitted abstract been presented or accepted for presentation at another meeting prior to the ACR submission deadline of May 3?** : No

Presentation Preference (Complete): Oral or Poster
Payment (Complete): Your credit card order has been processed on Tuesday 1 May 2007 at 8:48 AM.
Status: Complete

Control/Tracking Number: 07-A-1096-ACR
Activity: ACR Abstract Submission
Current Date/Time: 9/12/2007 10:51:54 AM

Significant Association between Changes in Glutamate Levels and fMRI BOLD Signal in the Posterior Insula of Fibromyalgia Patients

Author Block: Michael C. Hsu[1], Seong-Ho Kim[1], Pia C. Sundgren[2], Yuxi Pang[2], Richard H. Gracely[1], Daniel J. Clauw[1], Richard E. Harris[1]. [1]Rheumatology, University of Michigan, Ann Arbor, MI; [2]Radiology, University of Michigan, Ann Arbor, MI

Abstract:
Purpose: Previous functional neuroimaging studies in fibromyalga (FM) patients have shown augmented neural activity within the insula, a region involved in both sensory and affective pain processing. In a recent proton-spectroscopy (H-MRS) study, we found that glutamate (Glu) and/or glutamine levels in the right posterior insula appear to decrease with improvements in multiple pain dimensions within FM patients. These patients had also undergone fMRI as part of the study. We hypothesize that a decrease in fMRI BOLD signal within the right and/or left posterior insula would correlate with these changes in Glu levels, and also with improvements in clinical pain and evoked pain sensitivity.
Methods: As part of an ongoing trial of a non-pharmacological treatment in FM, 10 right-handed female patients (48+/- 15 yrs) underwent both fMRI and H-MRS prior to and following nine treatments. The H-MRS protocol was performed at rest, using single voxel spectroscopy (SVS) with a 2x2x3cm volume of interest placed over the right posterior insula. Using LCModel, levels of Glu were calculated as a ratio to the internal standard creatine (Cre). The fMRI protocol involved two 6.4-minute runs (256 scans each), during which varying amounts of discrete pressure were applied for 25 sec to the left thumbnail in fixed pseudorandom order, alternating with a no-pressure baseline, without producing post-ischemic pain. Images were processed with SPM2. The main effect of interest was the contrast between 0 and 2kg of pressure and how this contrast changed pre- vs. post- treatment. MarsBar was used to extract average BOLD contrast changes in statistically-significant regions of interest within the insula. Clinical and experimental pain were assessed pre- and post-treatment, with the Short Form McGill Pain questionnaire (SF-MPQ) and psychophysical pressure pain testing (multiple random staircase) respectively. Data were analyzed with SPSS v.14.
Results: A positive correlation was found between BOLD contrast changes in the left posterior insula (MNI coordinates {-42, -12, 0}) vs. pre- and post-treatment changes in Glu/Cre in the right posterior insula ($r = 0.801$, $p = 0.005$). Significant positive correlations were also found between these BOLD contrast changes and changes in SF-MPQ sensory ($r = 0.709$, $p = 0.022$) and SF-MPQ total ($r = 0.695$, $p = 0.026$) scores, but not experimental pain sensitivity. No other significant correlations were observed.
Conclusion: Changes in pain-induced fMRI BOLD contrast within the left posterior insula over time seem to correlate with changes in clinical pain intensity and varying Glu levels in the right posterior insula. A lack of sufficient statistical power may explain the absence of ipsilateral correlations between fMRI and H-MRS findings.
:

Author Disclosure Information: **M.C. Hsu**, None; **S. Kim**, None; **P.C. Sundgren**, None; **Y. Pang**, None; **R.H. Gracely**, Pierre Fabre, 5; Cypress BioScience, 5; **D.J. Clauw**, Department of Defense, Cooperative Agreement, 2; Cypress BioScience, 5; Lilly, 5; Forest, 5; Pfizer, 5; Wyeth, 5; **R.E. Harris**, Pfizer, Investigator

Initiated, 2.

Category (Complete): 9. Fibromyalgia and soft tissue disorder
Keywords (Complete): imaging techniques
Additional Keyword (Complete):
Eligibility (Complete):
***Has the data contained in the submitted abstract been presented or accepted for presentation at another meeting prior to the ACR submission deadline of May 3?** : No

Presentation Preference (Complete): Oral or Poster
Payment (Complete): Your credit card order has been processed on Tuesday 1 May 2007 at 3:41 PM.
Status: Complete

Control/Tracking Number: 07-A-1767-ACR
Activity: ACR Abstract Submission
Current Date/Time: 9/12/2007 10:44:33 AM

Musculoskeletal Symptoms and Signs Associated with Aromatase Inhibitor Therapy in Breast Cancer

Author Block: Monika Mohan[1], Dina Dadabhoy[1], Daniel J. Clauw[1], N. Lynn Henry[1], Daniel F. Hayes[1], Vered Stearns[2], Jon T. Giles[2], Anna Maria Storniolo[3], Dennis Ang[3]. [1]Rheumatology, University of Michigan, Ann Arbor, MI; [2]Johns Hopkins University, Baltimore, MD; [3]Indiana University, Indianapolis, IN

Abstract:
Background. AIs are increasingly used for the treatment of postmenopausal women with hormone receptor (HR)-positive breast cancer, but musculoskeletal side effects occur in up to 36% of patients. This toxicity has been poorly characterized to date, and its etiology is unknown.
Methods. Women with early stage HR-positive breast cancer are currently being accrued to a prospective multicenter randomized clinical trial of exemestane vs letrozole to study the pharmacogenomics of these two AIs. As part of this trial, a musculoskeletal sub-study was performed to better delineate the rheumatic symptoms associated with these drugs. Patients complete a Health Assessment Questionnaire and pain VAS at baseline, 1, 3, 6, 12, and 24 months (mo) to assess changes in pain and function during therapy. Those patients who exceed a pre-defined thresholds are referred for detailed rheumatologic evaluation, including physical exam and laboratory work. Planned overall accrual is 500. This report represents the first 100 patients, each with at least 6 months of follow-up.
Results. Of the first 100 patients enrolled, 38 of 41 who had new or significant worsening of existing musculoskeletal symptoms have been evaluated. Patients have been on study for a median 11.8 mo (6.2-20.1 mo). No significant difference in baseline characteristics is evident between those who did and did not develop musculoskeletal symptoms, except for a trend toward more referrals in patients with diabetes. Median time to development of symptoms was 3 mo (1-12 mo). Based on clinical evaluation, most patients developed non-inflammatory regional or diffuse musculoskeletal symptoms, including trochaneteric burisits, anserine bursitis, and iliotibial band syndrome. 8 patients developed new or worsening carpal tunnel syndrome (CTS). Laboratory data, including C-reactive protein, rheumatoid factor, and anti-nuclear antibody, was unremarkable in those developing symptoms. Of 23 patients who have dropped out of the study, 13 did so because of musculoskeletal toxicity, and an additional 6 patients switched to a different AI.
Conclusions. Musculoskeletal side effects, including CTS, have a substantial impact on use of AIs for adjuvant therapy of breast cancer. Further study of the mechanisms underlying this toxicity should be conducted, in order to better predict which patients are at greater risk of developing symptoms and to determine how best to manage these symptoms.
:

Author Disclosure Information: **M. Mohan**, None; **D. Dadabhoy**, None; **D.J. Clauw**, Department of Defense, Cooperative Agreement, 2; Cypress BioScience, 5; Lilly, 5; Forest, 5; Pfizer, 5; Wyeth, 5; **N.L. Henry**, None; **D.F. Hayes**, None; **V. Stearns**, None; **J.T. Giles**, None; **A. Storniolo**, None; **D. Ang**, None.

Category (Complete): 9. Fibromyalgia and soft tissue disorder
Keywords (Complete): drug toxicity ; musculoskeletal disorders
Additional Keyword (Complete):

Eligibility (Complete):

***Has the data contained in the submitted abstract been presented or accepted for presentation at another meeting prior to the ACR submission deadline of May 3?** : No

Presentation Preference (Complete): Oral or Poster
Payment (Complete): Your credit card order has been processed on Tuesday 1 May 2007 at 1:40 PM.
Status: Complete

American College of Rheumatology
1800 Century Place, Suite 250
Atlanta, GA 30345
For technical support, email support@abstractsonline.com or call 217-398-1792

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

Print this Page for Your Records Close Window

Control/Tracking Number: 07-A-1090-ACR
Activity: ACR Abstract Submission
Current Date/Time: 9/12/2007 10:47:07 AM

Functional MRI (fMRI) of Pain Processing is Stable over Time in Fibromyalgia (FM) Patients without Changes in Clinical Status

Author Block: Rupal Patel, David A. Williams, Richard H. Gracely, Linda Skalski, Samantha J. Chriscinske, Gina Alesi, Daniel J. Clauw. Rheumatology, University of Michigan, Ann Arbor, MI

Abstract:
Purpose: Neuroimaging studies using painful stimuli have been helpful in identifying brain regions associated with augmented sensory and affective characteristics of pain processing in patients with FM. To date, these studies have examined FM patients at single points in time. We are not aware of any study that has performed fMRI of pain processing at two separate points in time in patients with FM, to look for stability of fMRI findings over time. Showing such stability would be helpful in establishing that fMRI might serve as a valid biomarker in FM and related conditions.
Methods: 9 female patients (mean age = 45) satisfying ACR criteria for FM were selected from a larger pre-existing dataset based on very little to no change from 0-12 week in clinical pain, using the Brief Pain Inventory (BPI). After each assessment with the BPI, each participant underwent standardized evoked pressure pain testing (EPP) and fMRI neuroimaging. During 10 minute fMRI sessions, pressures calibrated to evoke mild, moderate, and slightly intense pain were applied to the left thumb by a 1cm diameter probe, as was 2kg of pressure for all participants (the scans used for this study). Identical methods were used at both sessions. fMRI data were acquired by a GE3 Tesla scanner at 2.5s intervals. Analysis of the BOLD signal (head motion correction, slice timing correction, spatial smoothed 6mm FWHM, intensity normalization, conversion to standard coordinate system, statistical comparison of 2kg response at 12 weeks to baseline) was performed using Medx.
Results: During equal pressure conditions, patients who showed no change in clinical pain also showed no significant differences in fMRI results from baseline to 12 weeks. There were mild changes in several regions over time but none approached the corrected Z threshold of 3.64.
Conclusions: This study suggests that even over fairly long periods of time, fMRI of pain processing is relatively stable in FM patients in whom there is no significant change in clinical symptoms. Such stability over time is a desirable attribute of a biomarker.
:

Author Disclosure Information: **R. Patel**, None; **D.A. Williams**, NIH, 2; Cypress BioScience, 5; **R.H. Gracely**, Pierre Fabre, 5; Cypress BioScience, 5; **L. Skalski**, None; **S.J. Chriscinske**, None; **G. Alesi**, None; **D.J. Clauw**, Department of Defense, Cooperative Agreement, 2; Cypress BioScience, 5; Lilly, 5; Forest, 5; Pfizer, 5; Wyeth, 5.

Category (Complete): 9. Fibromyalgia and soft tissue disorder
Keywords (Complete): imaging techniques ; psychosocial factors
Additional Keyword (Complete):
Eligibility (Complete):
***Has the data contained in the submitted abstract been presented or accepted for presentation at**

another meeting prior to the ACR submission deadline of May 3? : No

Presentation Preference (Complete): Poster Only
Payment (Complete): Your credit card order has been processed on Friday 27 April 2007 at 2:20 PM.
Status: Complete

American College of Rheumatology
1800 Century Place, Suite 250
Atlanta, GA 30345
For technical support, email support@abstractsonline.com or call 217-398-1792

Print this Page for Your Records Close Window

Control/Tracking Number: 07-A-1377-ACR
Activity: ACR Abstract Submission
Current Date/Time: 9/12/2007 10:47:53 AM

Characteristics Associated with Neck Pain Persistence versus Recovery after Minor Motor Vehicle Collision

Author Block: D. Robinson[1], S. A. McLean[2], R. Swor[1], E. M. Zaleski[2], Y. Mistry[2], Schon S[2], M. R. Sochor[2], CRH Newton[3], I. Liberzon[4], D. J. Clauw[5]. [1]Emergency Medicine, William Beaumont Hospital, Royal Oak, MI; [2]Emergency Medicine, University of Michigan, Ann Arbor, MI; [3]Emergency Medicine, St. Joseph Mercy Hospital, Ann Arbor, MI; [4]Psychiatry, University of Michigan, Ann Arbor, MI; [5]Rheumatology, University of Michigan, Ann Arbor, MI

Abstract:
Purpose: Persistent musculoskeletal neck pain is common after minor motor vehicle collision (MVC). Little is known regarding characteristics that distinguish individuals who experience musculoskeletal neck pain symptom resolution versus persistence. We sought to compare individuals with neck pain symptoms in the emergency department (ED) who did and did not have persistent musculoskeletal neck pain 1 month after MVC.

Material and Methods: Patients being evaluated in the emergency department (ED) after MVC were recruited into an ongoing multicenter study that includes ED baseline assessment and 1 month follow-up evaluation. ED evaluation includes an assessment of demographic, health, psychological, and symptom factors. One month telephone follow-up evaluation includes an assessment of MVC-related neck pain. Those reporting neck pain severity $\geqslant$ 4 on a 0-10 numeric rating scale were defined as having moderate or severe pain. Descriptive analyses were used to compare individuals with initial neck pain symptoms with and without persistent moderate or severe neck pain.

Results: Of 126 enrolled patients evaluated to date at the 1 month time point, 41 (33%) had initial neck pain in the ED but no moderate or severe neck pain at 1 month, and 47 (37%) had initial neck pain in the ED and persistent moderate or severe neck pain. Table 1 displays characteristics that distinguished these two groups.
Conclusion: Demographic, symptom, and cognitive characteristics distinguish patients in whom initial neck pain symptoms do and do not resolve. More work is needed to understand the pathophysiology of neck pain persistence vs. recovery after MVC.

Table 1: Characteristics of those with Neck Pain Persistence vs. Recovery after Minor Motor Vehicle Collision

Characteristic	Recovered (n = 41)	Persistence (n = 47)	t (p) or χ^2 (p)
Age (years)	34.7 (13.6)	43.7 (15.2)	2.91 (.005)
Income $\leqslant$ $20,000	23%	37%	9.55 (.089)
Pre-MVC Depressive Symptoms (CES-D)	11.4 (9.8)	16.2 (13.7)	1.82 (.073)
Pre-MVC Anxiety Symptoms (STPI)	20.6 (2.0)	22.2 (4.0)	2.27 (.027)

ED Neck Pain Intensity	4.6 (2.0)	6.5 (2.1)	4.23 (<.0001)
Peritraumatic Distress (Peritraumatic Distress Scale)	19.6 (2.0)	23.8 (9.2)	2.08 (.041)
Research assistant rating of patient distress (initial rating)	1.6 (1.4)	3.0 (2.6)	3.03 (.003)
Patient certainty that they will recover (initial rating)	9.6 (.69)	8.4 (2.0)	3.80 (<.0001)
Feeling that the accident was another person's fault	65%	74%	3.15 (.207)

:

Author Disclosure Information: **D. Robinson**, None; **S.A. McLean**, None; **R. Swor**, None; **E.M. Zaleski**, None; **Y. Mistry**, None; **S. S**, None; **M.R. Sochor**, None; **C. Newton**, None; **I. Liberzon**, None; **D.J. Clauw**, Department of Defense, Cooperative Agreement, 2; Cypress BioScience, 5; Lilly, 5; Forest, 5; Pfizer, 5; Wyeth, 5.

Category (Complete): 9. Fibromyalgia and soft tissue disorder
Keywords (Complete): pain ; prognostic factors
Additional Keyword (Complete):
Eligibility (Complete):
***Has the data contained in the submitted abstract been presented or accepted for presentation at another meeting prior to the ACR submission deadline of May 3?** : No

Presentation Preference (Complete): Oral or Poster
Payment (Complete): Your credit card order has been processed on Monday 30 April 2007 at 10:25 AM.
Status: Complete

Control/Tracking Number: 07-A-1389-ACR
Activity: ACR Abstract Submission
Current Date/Time: 9/12/2007 10:45:31 AM

Predictors of Persistent Moderate or Severe Neck and/or Back Pain 1 and 6 Months after Minor Motor Vehicle Collision

Author Block: S. Schon[1], S. A. McLean[1], Y. Mistry[1], E. M. Zaleski[1], R. Swor[2], D. Robinson[2], M. R. Sochor[1], CRH Newton[3], I. Liberzon[4], D. J. Clauw[5]. [1]Emergency Medicine, University of Michigan, Ann Arbor, MI; [2]Emergency Medicine, William Beaumont Hospital, Royal Oak, MI; [3]Emergency Medicine, St. Joseph Mercy Hospital, Ann Arbor, MI; [4]Pscyhiatry, University of Michigan, Ann Arbor, MI; [5]Rheumatology, University of Michigan, Ann Arbor, MI

Abstract:
Purpose: Chronic musculoskeletal neck and back pain is common after motor vehicle collision (MVC), but the etiology remains poorly understood. The relative predictive utility of demographic, psychological, physiological, and initial symptom factors is not known.
Material and Methods: Patients being evaluated in the emergency department (ED) after MVC were recruited into an ongoing multicenter study that includes ED baseline assessment and 1 and 6 month follow-up evaluation. ED evaluation includes an assessment of demographic, health, psychological, symptom, and physiologic factors. One and 6 month telephone follow-up evaluation assessed the presence of MVC-related moderate or severe pain symptoms ($\geqslant$ 4 on a 0-10 numeric rating scale) in the neck and/or back. The best combination of predictive factors for moderate or severe neck and/or back pain at each follow-up point was selected via stepwise logistic regression modeling. Model utility was evaluated via receiver operating characteristic (ROC) curve analyses.
Results: To date, 1 month follow-up data is available on 126 participants, and 6 month follow-up data is available on 69. The optimal set of 1 month predictors were age, race, pre-MVC anxiety symptoms, intensity of neck pain in the ED, and heart rate divided by systolic blood pressure (a measure of baroreceptor function, which is associated with neurosensory processing). The optimal set of 6 month predictors were somatic symptoms prior to the ED visit, general health, dissociative symptoms at the time of the MVC, initial patient estimate of the time until physical recovery, and initial neck pain symptoms. ROC curves for these models are shown in figure 1.
Conclusion: These pilot data suggest that a relatively small number of baseline predictors provides excellent prediction of persistent musculoskeletal pain after MVC.

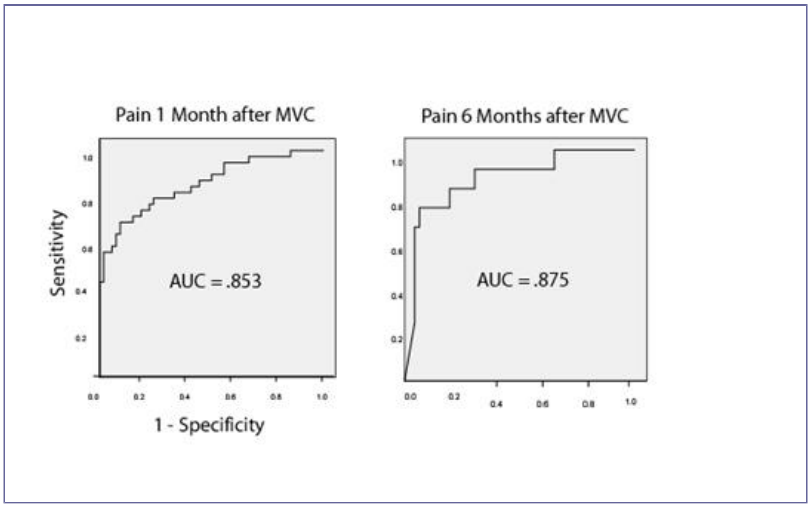


Figure 1 *:*

Author Disclosure Information: S. Schon, None; **S.A. McLean**, None; **Y. Mistry**, None; **E.M. Zaleski**, None; **R. Swor**, None; **D. Robinson**, None; **M.R. Sochor**, None; **C. Newton**, None; **I. Liberzon**, None; **D.J. Clauw**, Department of Defense, Cooperative Agreement, 2; Cypress BioScience, 5; Lilly, 5; Forest, 5; Pfizer, 5; Wyeth, 5.

Category (Complete): 9. Fibromyalgia and soft tissue disorder
Keywords (Complete): back pain ; prognostic factors
Additional Keyword (Complete):
Eligibility (Complete):
***Has the data contained in the submitted abstract been presented or accepted for presentation at another meeting prior to the ACR submission deadline of May 3?** : No

Presentation Preference (Complete): Oral or Poster
Payment (Complete): Your credit card order has been processed on Monday 30 April 2007 at 10:43 AM.
Status: Complete

American College of Rheumatology
1800 Century Place, Suite 250
Atlanta, GA 30345
For technical support, email support@abstractsonline.com or call 217-398-1792

Powered by OASIS, The Online Abstract Submission and Invitation System SM

Control/Tracking Number: 07-A-1394-ACR
Activity: ACR Abstract Submission
Current Date/Time: 9/12/2007 10:49:30 AM

Racial Disparity in Pain Outcomes after Minor Motor Vehicle Collision

Author Block: S. Schon[1], S. A. McLean[1], E. M. Zaleski[1], R. Swor[2], D. Robinson[2], Y. Mistry[1], M. R. Sochor[1], CRH Newton[3], I. Liberzon[4], D. J. Clauw[5]. [1]Emergency Medicine, University of Michigan, Ann Arbor, MI; [2]Emergency Medicine, William Beaumont Hospital, Royal Oak, MI; [3]Emergency Medicine, St. Joseph Mercy Hospital, Ann Arbor, MI; [4]Pyschiatry, University of Michigan, Ann Arbor, MI; [5]Rheumatology, University of Michigan, Ann Arbor, MI

Abstract:
Purpose: Chronic musculoskeletal pain is common after motor vehicle collision (MVC), but little data is available regarding the epidemiology of post-MVC pain outcomes. We examined whether racial disparities exist in musculoskeletal pain outcomes after MVC.
Material and Methods: Patients being evaluated in the emergency department (ED) after MVC were recruited into an ongoing multicenter study that includes ED baseline assessment and 1 month follow-up evaluation. ED evaluation includes an assessment of demographic, health, psychological, and symptom factors. One month telephone follow-up evaluation assessed the presence of MVC-related moderate or severe pain symptoms ($\geqslant$ 4 on a 0-10 numeric rating scale) in the neck or back. Descriptive, chi square, and logistic regression analyses were used to compare pain outcomes after MVC among African Americans and European Americans.
Results: Of 126 enrolled patients evaluated to date at the 1 month time point, 122 provided information regarding their race. Eighty-four (69%) were European American, 19 (16%) were African American, 7 (6%) were American Indian/Alaska native, 6 (5%) were Asian, and 6 (5%) were other/more than 1 race. African Americans were significantly more likely to have moderate or severe neck and/or back pain 1 month after MVC than European Americans (68% vs. 34%, p = .007). This difference persisted after adjustment for other demographic factors and known predictors of persistent pain: age, educational status, income, pre-MVC anxiety symptoms, and severity of initial neck pain symptoms in the ED (Wald = 4.2, p = .04).
Conclusion: African Americans may experience a higher incidence of moderate or severe neck or back pain after MVC than European Americans. Further work is needed to understand this racial disparity in musculoskeletal pain outcomes after minor MVC.
:

Author Disclosure Information: **S. Schon**, None; **S.A. McLean**, None; **E.M. Zaleski**, None; **R. Swor**, None; **D. Robinson**, None; **Y. Mistry**, None; **M.R. Sochor**, None; **C. Newton**, None; **I. Liberzon**, None; **D.J. Clauw**, Department of Defense, Cooperative Agreement, 2; Cypress BioScience, 5; Lilly, 5; Forest, 5; Pfizer, 5; Wyeth, 5.

Category (Complete): 9. Fibromyalgia and soft tissue disorder
Keywords (Complete): epidemiology ; race/ethnicity ; pain
Additional Keyword (Complete):
Eligibility (Complete):
***Has the data contained in the submitted abstract been presented or accepted for presentation at**

another meeting prior to the ACR submission deadline of May 3? : No

Presentation Preference (Complete): Oral or Poster
Payment (Complete): Your credit card order has been processed on Monday 30 April 2007 at 10:55 AM.
Status: Complete

American College of Rheumatology
1800 Century Place, Suite 250
Atlanta, GA 30345
For technical support, email support@abstractsonline.com or call 217-398-1792

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

Print this Page for Your Records Close Window

Control/Tracking Number: 07-A-1089-ACR
Activity: ACR Abstract Submission
Current Date/Time: 9/12/2007 10:48:47 AM

Functional MRI (fMRI) Appears to Act as a Biomarker in Fibromyalgia (FM) by Identifying Neurobiological Correlates of Changes in Pain Over Time

Author Block: David A. Williams, Rupal Patel, Linda Skalski, Samantha J. Chriscinske, Michael Rubens, Jeremy Lapedis, Richard E. Harris, Richard H. Gracely, Daniel J. Clauw. Rheumatology, University of Michigan, Ann Arbor, MI

Abstract:
Purpose: Previous fMRI studies using both pressure and heat stimuli have shown that FM is characterized by augmented central pain processing. To summarize, these studies have shown that with equal amounts of stimuli to controls, FM is characterized by augmented neuronal activity in regions of the brain associated with processing both sensory and affective stimuli. To date, these studies have been cross-sectional, and identified differences between patients and controls. The current study performed fMRI both before and after a behavioral intervention for FM, and compared neuronal activation patterns at baseline and post-treatment in a group with worsening clinical pain and a group that improved.
Methods: 18 female patients satisfying ACR criteria for FM were selected from a larger preexisting dataset based upon either improving or declining 0-12 week change scores in the Brief Pain Inventory (BPI). Group A had 12 patients (mean age = 45) with improvements in pain severity (1.92 U) and group B had 7 patients (mean age = 48) with worsening severity (1.93 U). After each assessment with the BPI, participants underwent standardized evoked pressure pain testing (EPP) and fMRI neuroimaging. During 10 minute fMRI sessions, pressures calibrated to evoke mild, moderate, and slightly intense pain were applied to the left thumb by a 1 cm diameter probe, as was 2kg of pressure for all participants (the scans used for this study). Identical methods were used at both sessions. fMRI data were acquired by a GE 3 Tesla scanner at 2.5s intervals and analysis of the BOLD signal was performed using Medx, correcting for multiple comparisons, using a region of interest analysis. Baseline activation data was subtracted from the 3-month data revealing regions of increased or decreased activity in response to identical stimuli over time.
Results: During equal pressure conditions, patients who showed *decreased* clinical pain severity, also showed significant *decreased* BOLD activity in brainstem, caudate, thalamus, putamen, inferior parietal lobule (BA 40), secondary somatosensory cortex, anterior cingulate cortex (BA 32 and BA 24), medial frontal gyrus (BA 6), and increased activity in only in the primary somatosensory cortex and middle frontal gyrus (BA 10). Patients whose pain *worsened* showed significant *increased* activity in insula, brainstem regions, inferior parietal lobule (BA40), middle frontal gyrus (BA 10) and decreased activity only in the middle frontal gyrus (BA 6).
Conclusions: These data suggest that increases or decreases in clinical pain in FM are associated with corresponding changes in neuronal activation patterns in brain regions involved in pain processing. These data suggest that fMRI may be able to serve as a biomarker in FM.
:

Author Disclosure Information: **D.A. Williams**, NIH, 2; Cypress BioScience, 5; **R. Patel**, None; **L. Skalski**, None; **S.J. Chriscinske**, None; **M. Rubens**, None; **J. Lapedis**, None; **R.E. Harris**, Pfizer, Investigator-initiated, 2; **R.H. Gracely**, Pierre Fabre, 5; Cypress BioScience, 5; **D.J. Clauw**, Department of Defense, Cooperative Agreement, 2; Cypress BioScience, 5; Lilly, 5; Forest, 5; Pfizer, 5; Wyeth, 5.

Category (Complete): 9. Fibromyalgia and soft tissue disorder
Keywords (Complete): imaging techniques ; biochemical markers
Additional Keyword (Complete):
Eligibility (Complete):
***Has the data contained in the submitted abstract been presented or accepted for presentation at another meeting prior to the ACR submission deadline of May 3?** : No

Presentation Preference (Complete): Oral or Poster
Payment (Complete): Your credit card order has been processed on Friday 27 April 2007 at 2:05 PM.
Status: Complete